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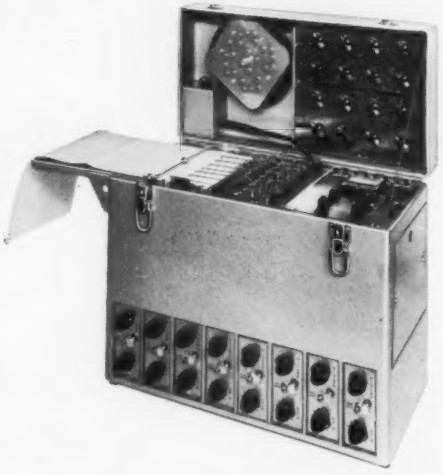

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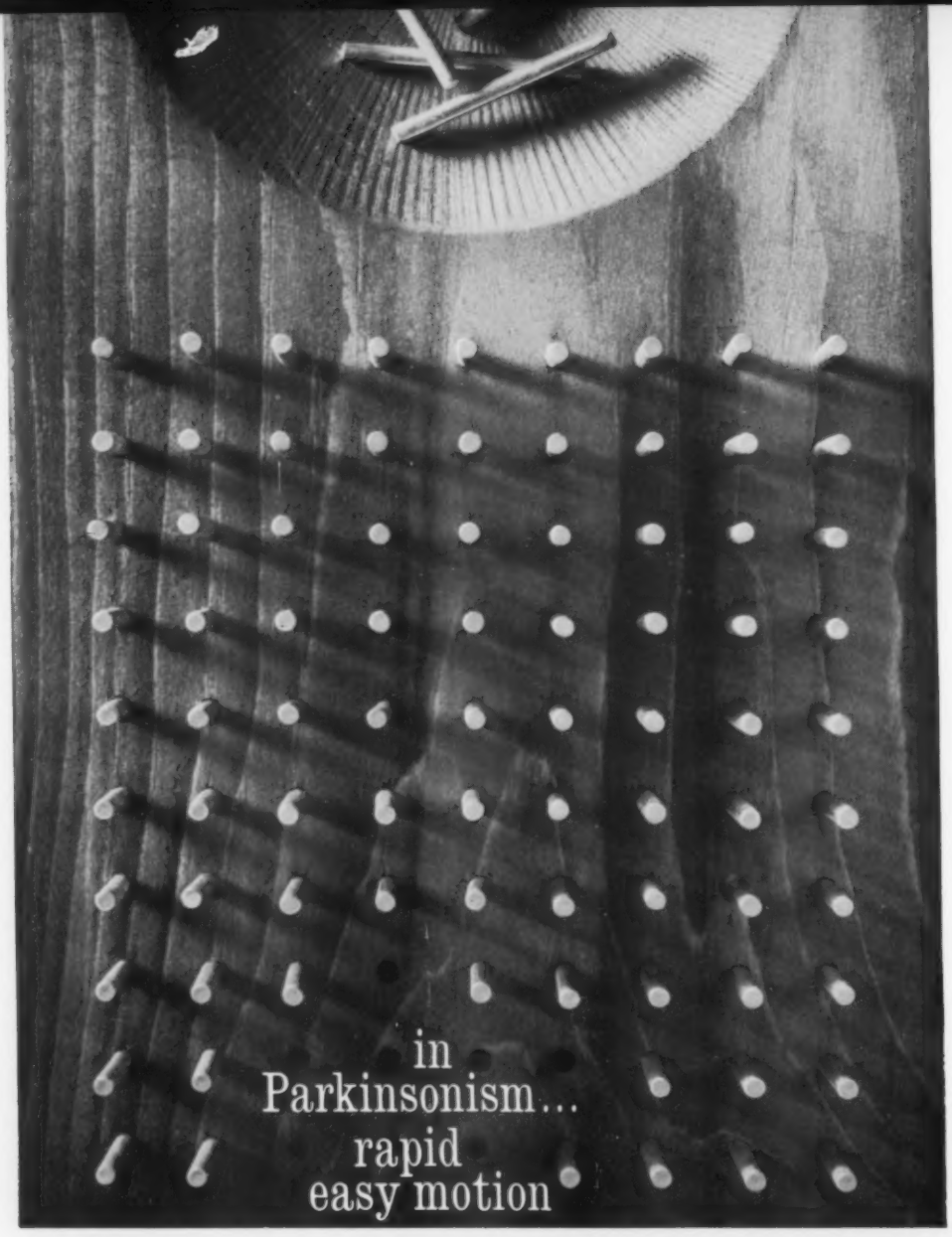

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A parkinsonian syndrome in the course of subacute encephalitis

M. J. Mossakowski, M.D., and G. Mathieson, M.B., Ch.B.

EXTRAPYRAMIDAL SYNDROMES form an essential element of the clinical picture of the subacute encephalitides of van Bogaert, Dawson, and Pette and Döring types.[1–6] They occur in the second phase of the disease, diminishing gradually with the increase of generalized decorticate rigidity which is typical of the terminal stage. These extrapyramidal syndromes usually take the form of simple or complex hyperkinesias. Muscle hypertonus is probably also partly extrapyramidal in origin during the second stage of the illness. Despite the remarkable variability of extrapyramidal syndromes occurring with the subacute encephalitides, a parkinsonian syndrome is rare. In the literature dealing with these 3 types of subacute encephalitis, we found only 1 case in which a parkinsonian syndrome temporarily dominated the clinical picture.[7]

We consider the following case of subacute sclerosing leukoencephalitis of van Bogaert interesting in that, during one phase of the disease, the patient showed a prominent parkinsonian syndrome. At one time, this was so dominant that the first diagnostic impression was "postencephalitic parkinsonism." However, the further course of the illness, including the development of a hyperkinetic syndrome characterized by rhythmic myoclonic jerks, and additional examinations such as electroencephalography and brain biopsy led to a correct diagnosis being established during the patient's life.

CLINICAL HISTORY

Mary P., age 11, was under clinical observation in Montreal Neurological Institute from March 11 to April 10, 1959. She was the second child in a sibship of 5. Her parents were young and healthy. There was no record of nervous or mental disease in the families of the father and mother. The siblings, 2 brothers and 2 sisters, were healthy and were of normal physical and mental development. The patient was born after a normal, full-term pregnancy. Delivery and early development were also normal. She started to walk at about 1 year and to speak between 2 and 3.

In September 1958, she had a brief illness called "flu," after which some slight, but gradually increasing change in her personality

From the Department of Neurology and Neurosurgery, McGill University, Montreal, and Montreal Neurological Institute.

Dr. Mossakowski is a fellow of the Polish Academy of Sciences, Warsaw.

developed. She cried easily and became disorderly and much less efficient in her school work. She became withdrawn and had some difficulty in her contacts with other children. Difficulty in learning increased rapidly so that, after two months, she was unable to continue at school. At the same time, marked slowness in movement and speech developed. Her gait became unsteady, and she often fell. She was unable to dress herself. Very often, she seemed to be in a "daze," and it was necessary to repeat questions several times before she noticed that she was being spoken to.

At the end of January 1959, rhythmic tremor of the hands was superimposed on the background of generalized motor slowness and marked mental deterioration. The tremor increased in extent and amplitude when she was excited. At the same time, difficulty in speaking developed; she did not speak spontaneously and answered questions with monosyllables. Her speech was slightly dysarthric. She had difficulty in swallowing.

In February 1959, she was admitted briefly to St. Rita's Hospital, Sydney, Nova Scotia. The outstanding neurologic abnormality found there was rigidity of all limbs and rhythmic tremor of both hands, increasing during voluntary movements. After discharge from hospital, her condition became worse. She was confined to bed, being scarcely able to walk; she was also unable to feed herself (Dr. Anne Earle).

Physical examination on admission to Montreal Neurological Institute on March 11, 1959, showed her to be well nourished and well developed. General physical examination was noncontributory. She lay in bed with an expressionless face and both hands drawn into the "main d'accoucheur" position. Her voice was high-pitched, monotonous, and indistinct. She was unable to carry out simple mental arithmetic, and there was other evidence of mental deterioration. The ocular fundi were normal. She had difficulty in swallowing and drooled saliva. Tone was increased in all muscle groups, with a cogwheel type of rigidity; this feature was more marked in the left arm and left leg. A pill-rolling tremor was present in both hands, more marked on the left, and was exaggerated by emotional stress. During voluntary movements such as closing the eyes, flexing the chin to the chest, and raising the head and shoulders, there was a generalized, violent tremor involving the whole body. Tendon reflexes were increased in both legs, and there was bilateral ankle clonus, but the plantar responses were flexor. No clear-cut evidence of cerebellar dysfunction was found. No sensory disturbance could be demonstrated.

During her stay in hospital, she remained confined to bed. With trihexyphenidyl (Artane) therapy, there was some improvement in her condition; her voice became stronger, swallowing improved, and drooling of saliva decreased. At the end of her first week in hospital, the clinical pattern changed dramatically. Tremor at rest, which had been a very prominent feature, disappeared completely. The rigidity changed, becoming more "lead pipe" than "cogwheel" in type. At about the same time, myoclonic jerks were seen for the first time; in these, both arms were raised, the eyelids blinked, and the legs were extended. Her muscle hypertonus continued to increase, so that by the third hospital week she was able to perform only very limited voluntary movements. Myoclonic jerks increased in frequency and severity. She was discharged on April 10, 1959. Thereafter, her condition rapidly deteriorated and she died twelve days later, eight months after the onset of her final illness.

Laboratory investigations. The urine was free from phenylketones, and metachromatic bodies were not found on microscopic examination. Hematologic and biochemical studies showed no significant abnormality. Cerebrospinal fluid was at normal pressure and clear and contained 26 mg. per cent protein and 2 lymphocytes per cubic millimeter; the Lange read 5533210000. Plain roentgenograms of the skull showed no abnormality. A pneumoencephalogram showed slight symmetric enlargement of the lateral ventricles.

On electroencephalograms (Fig. 1) made March 11, 1959, the most striking abnormality was seen in the sleep record. This consisted of bilaterally synchronous, high-voltage sharp waves, maximum in anterior head regions, interrupted by stretches of low-voltage activity. The sharp waves often occurred in groups separated by stretches of low-voltage activity, the pattern resembling that described as a suppression-burst activity. Sometimes, instead of bursts of sharp waves, there were bursts

Fig. 1. Sample of first electroencephalogram (March 11, 1959). Bipolar recording on Grass 8-channel machine. F4-C4=Right midfrontal to right midcentral. C4-P4=Right midcentral to right midparietal. P4-O2=Right midparietal to right occipital. F3-C3=Left midfrontal to left midcentral. C3-P3=Left midcentral to left midparietal. P3-O1=Left midparietal to left occipital. T4-CZ=Right midtemporal to central vertex. CZ-T3=Central vertex to left midtemporal

of slow waves, or slow and sharp waves mixed together. During wakefulness, the activity was not quite so severely disturbed but was still abnormal, with some bilateral, synchronous, high-voltage, slow and sharp wave discharges and some disturbance of regulation of cortical rhythms. These findings indicated the presence of diffuse, bilateral, brain abnormality involving cortical and subcortical structures.

A subsequent electroencephalogram on April 3 (Fig. 2) showed a definite deterioration, indicating a marked progression of the disease. In the waking stage, the background activity was rather flat with some rapid rhythms but hardly any alpha activity, which was reduced to insignificant remnants in the occipital region. Superimposed upon this background were bursts of bilateral, synchronous, irregular, high-voltage slow waves which occurred at intervals varying between about eight and sixteen seconds. Occasionally, some sharp wave discharges were associated with these slow waves. The paroxysmal slow wave discharges were associated with generalized movements of the limbs only in the waking state, although the paroxysmal slow wave discharges still occurred during sleep when movements were absent. In contrast to the first tracing, the second electroencephalogram in the waking state showed more abnormality than during sleep. During sleep, there were some remnants of normal potentials, whereas the background activity during wakefulness was entirely abnormal. The electroencephalographic pattern was considered to be typical of inclusion body encephalitis or the van Bogaert type of sub-

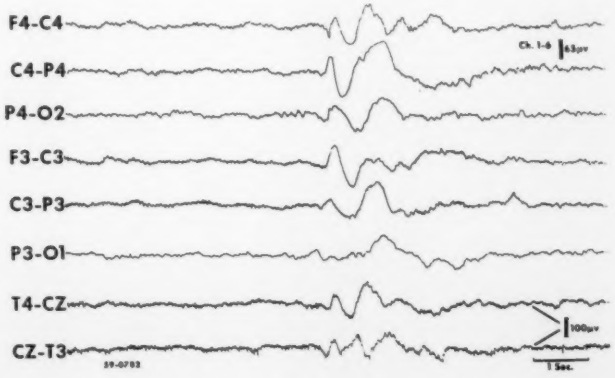

Fig. 2. Sample of second electroencephalogram (April 3, 1959). Technical data as in Figure 1

acute sclerosing leukoencephalitis (Dr. Peter Gloor).

Brain biopsy was carried out on March 18. The specimen, from the left parietooccipital region, contained both cortex and subcortical white matter. Perivascular infiltration by lymphocytes and some plasma cells in both the cortex and white matter was seen, more profuse in the white matter. Diffuse proliferation of microglial cells was noted throughout the cortex; most of them had hypertrophied, rod-shaped nuclei. Also, slight astrocytic proliferation was found, mainly in the deeper cortical layers. Most of the neurons appeared normal, but there were some rare examples of shrinkage and disintegration of neurons associated with satellitosis. Inclusion bodies were not seen. In the white matter, there was diffuse fibrogliosis associated with hypertrophy of astrocytes. Myelin damage was not seen. No metachromatic deposits were found in the white matter. The histopathologic features were those of subacute encephalitis, and the preferential involvement of the white matter favored the diagnosis of van Bogaert's subacute sclerosing leukoencephalitis.

Virologic studies by Dr. A. M. Masson of the blood, cerebrospinal fluid, stool, and brain specimen were negative.

PATHOLOGIC OBSERVATIONS

General autopsy was carried out in St. Rita's Hospital in Sydney, Nova Scotia, by Dr. A. W. Cyorfi, to whom we are indebted for the pathologic material. The trunk organs showed no significant abnormality on gross examination. Microscopic examination showed only patchy areas of terminal bronchopneumonia bilaterally.

The brain was small but symmetric and normal in form externally. However, there was marked firmness of the cerebrum, cerebellum, and brain stem. On section, no focal lesion was seen other than at the site of biopsy. Demyelination could not be detected on naked eye examination. The substantia nigra appeared wholly unpigmented. The locus coeruleus could be made out but was only very faintly pigmented. The basal ganglia, thalamus, subthalamic nuclei, dentate nuclei, and inferior olives appeared normal. The ventricular system was not dilated.

Histopathology of the brain. The leptomeninges contained discrete perivascular cuffs of lymphocytes and plasma cells. The cortex showed diffuse, inflammatory change occurring mainly in the form of perivascular infiltrates, which were, however, not profuse, being confined to 3 or 4 layers of lymphocytes and plasma cells surrounding small, otherwise normal, cortical blood vessels (Fig. 3). Although perivascular infiltration was present throughout the cortex, it tended to occur mainly in the deep cortical layers and at the cortical–white matter junction. There was intense microglial proliferation both diffuse and nodular, the latter involving mainly the deeper cortical layers (Fig. 4). Moderate prolifer-

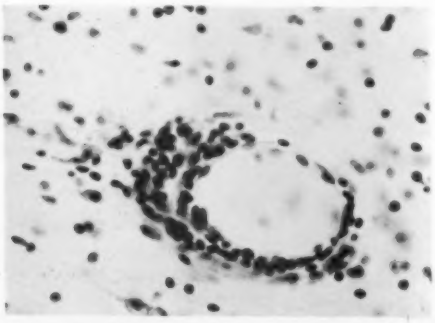

Fig. 3. Right temporal cortex showing venule surrounded by lymphocytes and plasma cells. Cresyl violet stain. × 360

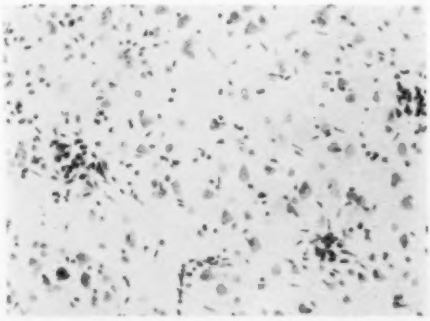

Fig. 4. Right temporal cortex showing diffuse and nodular microglial proliferation. Cresyl violet stain. × 120

ation of fibrillary astroglia was also seen, occurring mainly near the junction of cortex and white matter. Neurons were but little involved; there was, however, slight patchy neuronal loss in all cortical layers, perhaps more definite in the third and fifth layers. Some neurons showed shrinkage and hyperchromatism of the cell body or chromatolysis, the latter change being more common. Neither intranuclear nor cytoplasmic inclusions were found. These features were present in all cortical regions; temporal and parietal cortex were most involved, frontal and insular least.

The cerebral white matter also showed perivascular infiltration with lymphocytes and plasma cells; these were more intense than in the cortex. The left temporal and parietal lobes seemed to be most severely involved. The myelin picture in most areas appeared normal, but, in the anterior limb of the internal capsule, there was some patchy pallor of myelin and, in the left occipital lobe, several small, ill-defined foci of myelin breakdown were present. In some of these the myelinated fibers of the cortex were also involved. In the areas of myelin damage, Sudan IV stained frozen sections showed fine, granular, sudanophilic deposits lying free in the tissue and occasionally accumulated in perivascular spaces. There were only occasional fat-laden macrophages.

Diffuse, dense fibrogliosis of the whole cerebral white matter was the most prominent feature histopathologically (Fig. 5). This fibrogliosis was out of proportion to the myelin damage and occurred in many places where myelin appeared entirely normal. It reached its greatest intensity in the temporal and parietal lobes and in the extreme and external capsules. The internal capsules and the corpus callosum were only slightly involved. Some proliferation and hypertrophy of microglial cells were also seen in the white matter, but only occasional small nodules and glial stars were observed here.

Perivascular inflammatory sleeves were prominent in the striatum, pallidum, and nucleus subthalamicus Luysii. There was some diffuse and nodular microglial proliferation in these structures, but it was less in degree than in the cortex. Several putaminal neurons appeared pale, but there was no definite neuronal loss or fibroglial proliferation here. Severe

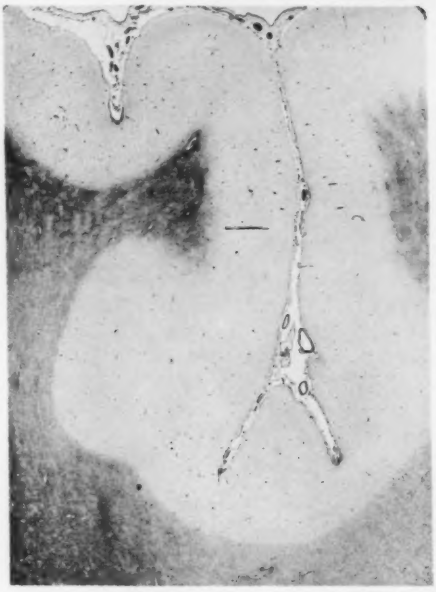

Fig. 5. Left frontal lobe showing diffuse fibrogliosis of white matter. Holzer's method. × 5

pathologic changes were seen in the thalamus and lateral geniculate bodies. These structures, besides perivascular cuffs and diffuse and nodular microglial proliferation, showed severe neuronal loss and accompanying fibrogliosis. Severe damage of the substantia nigra was the outstanding pathologic change in the midbrain. This structure had lost many of its neurons, especially in its lateral and central groups (Fig. 6), while the medial group appeared more or less normal. The surviving nigral neurons showed various signs of damage; many were shrunken, deformed, or fragmented (Fig. 7), and others showed pigment loss and tigrolysis. Melanin granules lay free in the tissue, but phagocytosis of melanin was not a feature. The neuronal loss had produced much rarefaction of the tissue, the small holes resulting from the disappearance of neurons being surrounded by microglial cells. There were rare examples of neuronophagia. These parenchymal changes were accompanied by marked astrocytic and microglial proliferation, the former being more intense. Holzer stain

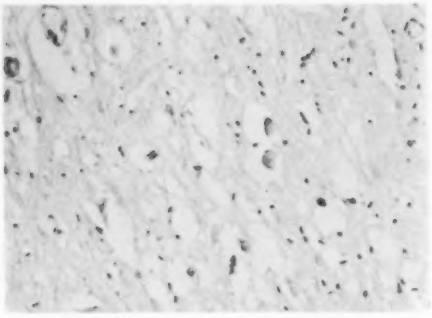

Fig. 6. Substantia nigra showing fenestration of tissue resulting from loss of neurons. Hematoxylin and eosin. × 110

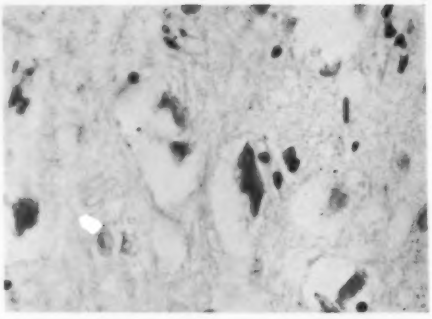

Fig. 7. Substantia nigra, higher magnification, showing damage to residual neurons. Hematoxylin and eosin. × 360

revealed selective fibrogliosis of the substantia nigra (Fig. 8). All these changes involved both rostral and caudal portions of the substantia nigra. The rest of the midbrain, including the red nucleus and tectal region, was the site of minimal perivascular cuffing accompanied by moderate microglial proliferation. The tegmental portion of the pons presented a similar picture, while more abundant perivascular infiltration, microglial proliferation, and some neuronal loss were seen in the basal portion of the pons. The locus coeruleus showed a normal neuronal population with slight glial proliferation.

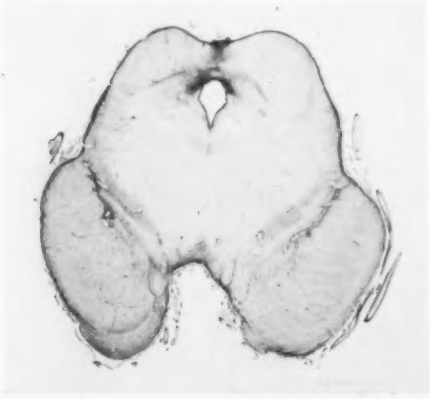

Fig. 8. Midbrain showing selective fibrogliosis in central and lateral groups of substantia nigra. Holzer's method. × 2.3

The medulla appeared normal apart from minimal perivascular infiltration in the subependymal region and isolated microglial nodules in the inferior olives. In the cerebellum, scanty perivascular cuffs and nodular glial proliferation in the dentate nuclei were accompanied by moderate fibrogliosis of the white matter.

In summary, the brain showed widespread inflammatory features. Fibrogliosis out of proportion to the myelin damage had occurred in the cerebral white matter. The substantia nigra was severely damaged, while, more caudally, changes were slight. Neither neuronal nor glial inclusion bodies were found. A diagnosis of subacute sclerosing leukoencephalitis of van Bogaert type was made.

DISCUSSION

According to the accounts of van Bogaert, Brain, and others, 3 main phases are distinguishable in the disease. At the onset, impaired intellectual ability and abnormalities of behavior occur and gradually progress, so that latterly there is profound dementia. The second phase of the illness is dominated by motor disturbances in the form of extrapyramidal syndromes. Finally, the patient passes into a decorticate state. In our case, the second period of the disease presented an interesting and unusual picture. In this phase of extrapyramidal symptomatology, we can distinguish 2 well defined subphases. During the first of these, lasting approximately two months, there was a striking parkinsonian syndrome which

later disappeared, being replaced in the second phase by a hyperkinetic syndrome dominated by generalized, myoclonic discharges. The earlier clinical picture presented the complete triad of parkinsonian symptomatology—akinesia, muscular rigidity of cogwheel type, and tremor at rest. There were, however, no oculogyric crises or vegetative disturbances, but difficulty in articulation and swallowing occurred. It is noteworthy that all these symptoms improved with medication. In addition to the typically parkinsonian rest tremor, we observed some intention tremor. Carpenter[8] pointed out the difficulty in separating these 2 types of tremor in the course of Parkinson's syndrome, the tremor at rest often being accompanied by one of intention type. The generalized irregular trembling of the patient's whole body, which occurred during some voluntary movements, was, in our opinion, a quite different clinical phenomenon. We consider it to be a particular form of the generalized motor discharges described by Macken and Lhermitte,[9] Martin and Isler,[10] and Weingarten and Seitelberger.[7]

While many different extrapyramidal symptoms have been described with the subacute encephalitides and the individual elements of Parkinson's syndrome are commonly reported, a fully established parkinsonian syndrome is rare. We have reviewed the literature on subacute encephalitis from this point of view. In 66 cases of sclerosing leukoencephalitis of van Bogaert culled from the literature[1,7,9–24] and in 1 previous unpublished case of our own, 21 patients had some form of tremor. Unfortunately, in most cases, the precise characteristics of the tremor were not described. In some cases,[7,9,10] the tremor occurred in the form of local or generalized paroxysmal motor discharges. In 1 case published by Corsellis[14] and in 1 of the Poser and Radermecker series,[19] the tremor was described as being of intention type. In 4 cases (those of Macken and Lhermitte[9] and Weingarten and Seitelberger[7]), a parkinsonian type of tremor occurred. In 24 published cases of subacute inclusion encephalitis of Dawson type,[3–5,25–29] 7 were described as having tremor; in 3, the tremor was not clearly described, and, in 2,[13,26] the tremor was parkinsonian in type, occurring at rest and disappearing during voluntary movement. In 29 cases of panencephalitis nodosa,[6,30–38] only 2 patients (both from Kalm's series[32]) are described as having tremor; in each, the tremor occurred at rest.

Muscular hypertonus is a constant clinical feature in the course of subacute encephalitis. According to most authors, it is partly extrapyramidal in nature, but Foley and Williams[26] have emphasized that rigidity of classical parkinsonian type is exceptional. Akinesia, the third major element of Parkinson's syndrome, is probably complex in origin. Poverty of facial expression, commonly seen with sclerosing leukoencephalitis,[1,10,13] subacute inclusion encephalitis,[3,13] and panencephalitis nodosa,[6] could be attributed to akinesia of a parkinsonian nature, but, undoubtedly, in many cases mental changes play a part in its production.

In only 1 case of subacute sclerosing leukoencephalitis, that of Weingarten and Seitelberger,[7] have all 3 parkinsonian elements been observed together. They occurred in a 13-year-old girl with a clinical diagnosis of parkinsonism. She was observed by the authors themselves only in the terminal period of the disease when the parkinsonian features had disappeared, and all information about the earlier symptomatology was indirect. In all other cases of subacute sclerosing leukoencephalitis that we found in the literature, only some elements of the parkinsonian syndrome were observed as discussed above. The same is true of cases of inclusion body encephalitis[3,4] and of panencephalitis nodosa.[32]

Histopathologic examination in our case revealed much damage to the substantia nigra. This was especially severe in the lateral and middle neuronal groups of the nucleus, while the medial group was relatively spared. This distribution of lesions corresponds in general to that described by Hassler[39] as typical of "idiopathic" Parkinson's disease. It seems reasonable, therefore, to attribute the parkinsonian syndrome in our case to involvement of this structure. The substantia nigra is commonly involved in subacute sclerosing leukoencephalitis. Guazzi,[40] studying the topography of lesions in the brain stem in 50 cases at the Institute Bunge, found severe neuronal loss in the substantia nigra in 14 cases. Nevertheless, none of these patients manifested a

pure parkinsonian syndrome clinically.[41] Similarly, of the 24 patients with subacute inclusion encephalitis reviewed above, 9 had changes in the substantia nigra. In panencephalitis nodosa, 7 of 29 cases in the literature had nigral lesions, although in this condition neuronal destruction was less marked. The question arises then, why, with nigral lesions so frequent in subacute encephalitis, has a parkinsonian syndrome been seen in only 1 previous case and what factor determined its occurrence in this present case? It is probable that the disease process must involve a sufficiently large proportion of the neuronal population of the nucleus before the clinical syndrome becomes manifest. This in itself does not appear to be an adequate explanation, as in many cases without parkinsonian features the nigral lesion has been described as severe. We believe that parkinsonian symptomatology will only occur in cases in which sufficiently severe damage to the substantia nigra (or related structures) takes place early in the course of the disease. In those cases in which nigral damage occurs late, after other structures producing hyperkinetic symptoms have been damaged, the alteration of the substantia nigra can be clinically mute, masked by hyperkinetic symptomatology. The histopathologic changes, especially the intense fibrogliosis, in our case indicate that the damage to the substantia nigra occurred rather early in the course of the disease. Later involvement of other structures of the central nervous system caused the dramatic change in the clinical picture.

The converse situation in which a parkinsonian syndrome[7] or prominent elements of this syndrome[9,13] occur in subacute sclerosing leukoencephalitis without a nigral lesion calls for comment. These cases can only be explained by supposing that extranigral lesions are responsible for the parkinsonian features. That such an event may occur is supported by the observations of Coërs, Kleyntjens, and Brihaye[42] on parkinsonian symptoms in cases of intracranial tumor in which the substantia nigra was intact. Recently, Dr. J. Gybels in our department has studied a case of sphenoidal ridge meningioma presenting exactly these features.

The question of similarities and differences and of possible essential identity of the different forms of the subacute encephalitides has been discussed by the majority of authors quoted and others[43–45] on clinical, electroencephalographic, and pathologic grounds. Considering the almost indistinguishable clinical picture and very similar pathologic changes in the 3 forms of subacute encephalitides, we agree with the widespread opinion that further morphologic discussion on their identity or otherwise will not solve the problem. Only etologic data will answer this question.

SUMMARY

1. A clinical and pathologic account of a case of subacute sclerosing leukoencephalitis of van Bogaert with a prominent Parkinson's syndrome at one stage of the illness is presented.

2. The morphologic basis of this clinical syndrome, rare in the course of subacute encephalitis, is discussed and the relevant literature reviewed.

The authors are indebted to Dr. Francis McNaughton and Dr. Ludo van Bogaert for their interest and advice.

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Experimental cretinism in rats

Electron microscopic observations on axonal changes

Kenneth R. Smith, Jr., M.D.

THE MICROSCOPIC ANATOMY of the cerebellum of human cretins was described by Lotmar[1] in 1933. He observed that the Purkinje cells were displaced into the molecular layer and were of bizarre configuration and stainability. More recently, Erbslöh[2] also has reviewed the pathologic histology of the central nervous system in cretins. During the past decade, Eayrs and associates have studied brains of rats made cretinous by injections of thiouracil or radioactive iodine soon after birth. Their findings plus most of the literature pertaining to the central nervous system in experimental cretinism and hypothyroidism were reviewed by Eayrs in 1955.[3] The most striking findings have been a reduction in the size of the neurons, in the number of axons, and in the amount of myelin, as well as decreased branching of dendrites and an apparent increase in intercellular space.

The present investigation was undertaken in order to determine the ultrastructure of the central nervous system of rats experimentally made cretinous. This report concerns one striking finding which has been observed in the cerebellum—an abnormal form of axoplasm in the large myelinated axons of the granular layer.

MATERIAL AND METHODS

Pregnant albino rats were given 0.1% propylthiouracil in their drinking water from the first week of pregnancy throughout pregnancy and lactation. Their offspring were decapitated one to thirty-five days after birth. At all ages, these rats were smaller and feebler than controls. Their appearance was characteristic of cretins as described by Hughes,[4] with blunt noses, stubby tails, and puffy skin as the dominant features. The tissues were routinely prepared for electron microscopy by fixation in Dalton's chrome-osmium solution, dehydration in ethanol, and embedding in methacrylate; thin sections were cut with glass knives in a Porter-Blum microtome. The sections were examined in an RCA EMU-2B or 2E electron microscope.

OBSERVATIONS

Controls. The fine structure of normal axoplasm has been described by Luse[5] and Vial,[6] among others. Axoplasm normally consists of an electron-lucent matrix containing occasional mitochondria, a varying number of neurofilaments, and some particles of small size. It contains little, if any, ergastoplasm (endoplasmic reticulum) or Golgi material.

Experimental. Sections of the cerebellums taken from 5 rats 30 to 35 days of age contained scattered abnormal myelinated axons in the granular layer. Only large myelinated fibers were affected. Sections of similar areas from younger cretins and from controls 30 to 40 days old contained no such altered axons. In the axons of the white matter adjacent to the peculiar axons, no abnormalities were seen (Fig. 1). It is impossible at this time to determine the cell of origin of the pathologic axons; they probably were either mossy fibers (axons of cells outside the cerebellum which end in the glomeruli of the granular layer) or axons of Purkinje cells.

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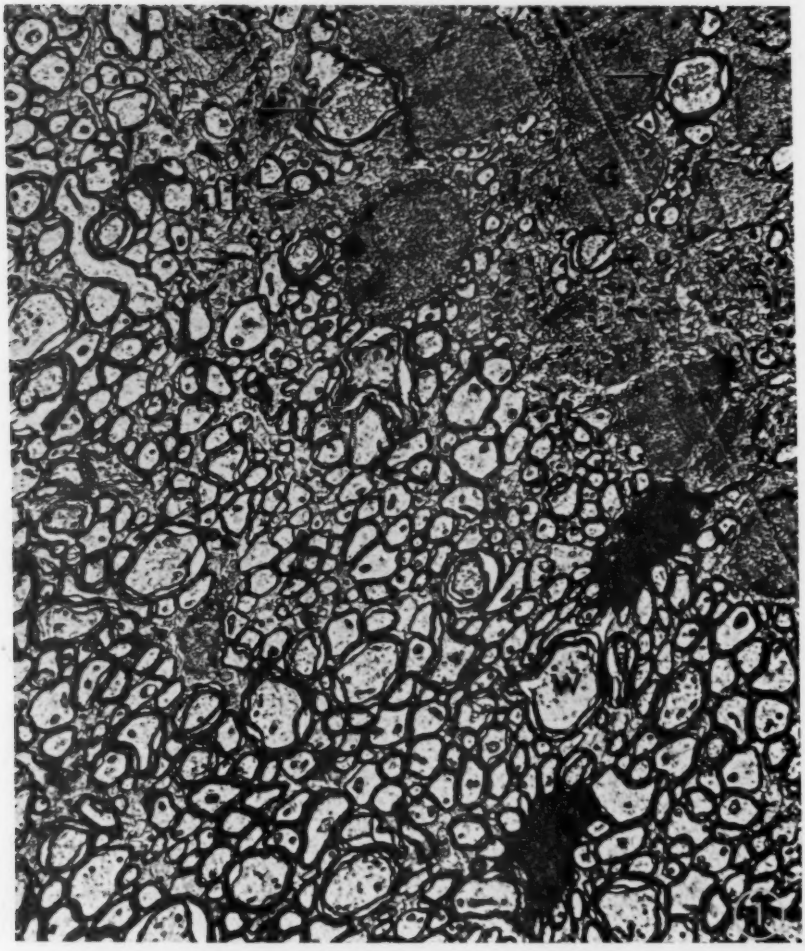

Fig. 1. 35-day-old cretin rat cerebellum. Low-power view of junction of white matter and granular layer with granule cells (G) at upper right and white matter made up of myelinated fibers (W) at lower right; 2 axons (arrows) in granular layer contain abnormal membranous material. None of axons in white matter contain these inclusions. × 4,600

Some large myelinated axons in the granular layer contained masses of membranous material filling almost the entire sectioned area of the fibers (Figs. 2 and 3). A few of the axons were dilated where the abnormal membranous accumulations were present, which suggested that the changes were present as focal nodules within the axon rather than filling long segments of the fiber. Other axons did not appear to be dilated. Myelin preservation was not particularly satisfactory in either the control or experimental material, but no gross defects were seen in myelin surrounding the areas of abnormal axoplasm or

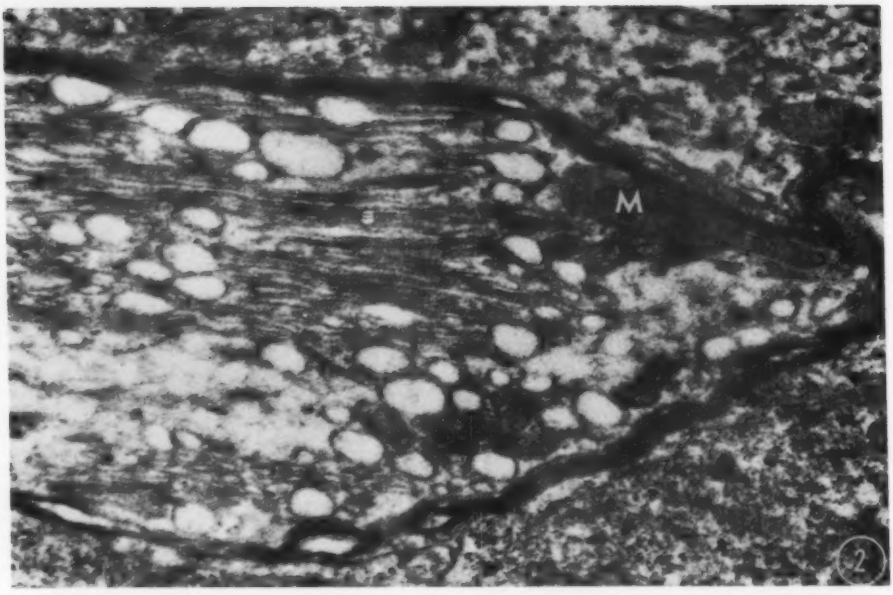

Fig. 2. 35-day-old cretin rat cerebellum. Large myelinated axon in granular layer is cut in longitudinal section. Most of axoplasm is made up of abnormal membranes forming tubules with bulbous dilations usually located at ends of tubules. Normal mitochondrion is present (M). × 32,000

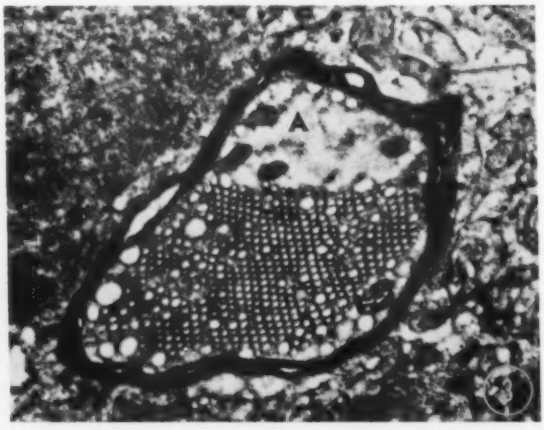

Fig. 3. 35-day-old cretin rat cerebellum. Large myelinated axon in granular layer is cut in cross section. It contains small sector of normal axoplasm (A) and large accumulation of membranous inclusions packed tightly together. × 18,000

elsewhere. When cut in longitudinal sections, the abnormal axoplasm appeared to be composed of membranes arranged in long tubes with bulbous dilations at the ends (Fig. 2). On cross sections, the material had the appearance of many small rings, often packed tightly together, filling one-half to three-fourths of the fiber with the remaining axoplasm being of normal appearance (Fig. 3). Sometimes, the membranes were less tightly packed, with occasional mitochondria and small particles intermingled among them (Fig. 2).

DISCUSSION

Abnormalities of the axoplasm of cretins have not been described by light microscopists.[1–3] Their preparations may not have contained such changes as were seen in this investigation, but it is possible that the magnifications used were not great enough to reveal them. (After recognition of these abnormal axons in the electron microscope, it was possible to go back and pick out some of them in thick sections of methacrylate-embedded tissue using the oil immersion lens of a phase contrast microscope. No routine light microscopy examinations have been made.) Too few animals have been examined to confirm or deny the findings of Lotmar,[1] Erbslöh,[2] and Eayrs.[3]

No membranous inclusions identical with those seen in this investigation have been described by electron microscopists. Axons undergoing Wallerian degeneration[6,7] contain clumps of altered mitochondria and axoplasm but no inclusions such as these. Such inclusions have not been seen by Luse[8] in degenerating axons of hereditarily ataxic rabbits.[9] They could be a form of the myelin figures which have been described in various cells under differing conditions.[5,10] However, previously described myelin figures have been nonspecific whorls or concentric rings or spheres of degenerating lipoprotein and not tubular membranes packed together, as seen in these cretinous rats. Thus, the origin and significance of this abnormal axoplasm remain obscure. This finding does perhaps help to explain the ataxia and impaired righting reflexes of cretinous rats described by Hughes.[4]

SUMMARY

Electron microscopy has revealed membranous inclusions in the large myelinated axons in the granular layer of the cerebellar cortex of rats made cretinous by propylthiouracil. This type of inclusion has not been described before, and its significance is unknown at this time.

Propylthiouracil was supplied by Lederle Laboratories.

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Genetics of convulsive disorders

II. Genetic and electroencephalographic studies in centrencephalic epilepsy

Katherine Metrakos, M.D., and Julius D. Metrakos, Ph.D.

IN THE FIRST PAPER of this series,[1] we presented and discussed, chiefly from a geneticist's point of view, a few of the problems inherent in a genetic study of a category as heterogeneous as convulsive disorders. In that earlier paper, the prevalence of individuals who had had at least one convulsion, irrespective of cause, among the near relatives of affected children was compared with that among the relatives of unaffected children. From the preliminary data summarized in Table 1, it was concluded [1] that there is strong evidence for a familial distribution of convulsions and [2] that it would probably be possible, on the basis of clinical and electroencephalographic criteria, to delineate specific genetic subgroups within the various epilepsies.

WHAT'S IN A NAME?

Reports in support of hereditary factors in epilepsy date back at least to biblical times. Even a modest perusal of these reports would be a mammoth task indeed. Fortunately, extensive reviews of this particular literature can be found in the writings of Alström,[2] Harvald,[3] and Lennox,[4] to mention but a few of the more recent ones.

The findings of the earlier as well as the more recent investigators suggest that, if hereditary factors underly some of the epilepsies, this is most likely to be demonstrated when the proband has no apparent extrinsic cause for his epilepsy. And, to hide our ignorance here, we say that the patient has idiopathic epilepsy. But neither the word idiopathic nor its many synonyms—asymptomatic, cryptogenetic, cryptogenic, endogenous, essential, familial, genetic, genuine, hereditary, intrinsic, metabolic, petit mal, and the rest—describe a specific type of epilepsy. In point of fact, not all of these terms are synonymous, for there is considerable variation as to what the original authors included under the particular term favored by them. For example, approximately two-thirds of all epileptic persons have no known cause for their epilepsy, and we may, as is usually done, refer to this as idiopathic epilepsy. However, if the type of seizure is employed as a criterion of classification, only a small portion of these patients will have the characteristic eye-blinking, head-nodding and momentary absences that are associated with typical petit mal epilepsy. Furthermore, the typical paroxysmal bilaterally synchronous 3-per-second wave-and-spike in the electroencephalogram will certainly not be found in all of the patients who were classed as having petit mal on clinical grounds. Many of these terms, and particularly the term familial, are used only when there is a positive family history for convulsions. When one is attempting to evaluate hereditary factors, this practice is of course thoroughly catastrophic. A large portion of this terminology is clothed in antiquity and mysticism. For example, the words cryptogenetic, genuine, and intrinsic are often used as if they implied something mystical about the nature and mode of action of hereditary factors. And, finally, the term asymptomatic is an outright misnomer, for a patient with convulsions is certainly not symptom-free.

In 1950, at the thirtieth meeting of the Association for Research in Nervous and Mental Diseases, Dr. Wilder Penfield[5] proposed the word *centrencephalic* "to identify that

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TABLE 1
PREVALENCE OF INDIVIDUALS WITH CONVULSIONS AMONG THE NEAR RELATIVES OF A HETEROGENEOUS GROUP OF 68 AFFECTED CONVULSANT PROBANDS AND THE NEAR RELATIVES OF 132 UNAFFECTED CONTROL PROBANDS

Relationship to proband	*Convulsant*		*Control*		*P*
	Number	*% affected*	*Number*	*% affected*	
Parents	136	9.56 ± 2.53	264	2.27 ± 0.89	.002*
Siblings	104	9.61 ± 2.90	325	3.38 ± 1.00	.005*
Aunts and uncles	706	5.81 ± 0.89	1,298	2.31 ± 0.45	.001*
Grandparents	272	1.47 ± 0.71	528	0.57 ± 0.32	.130
Cousins	1,022	1.66 ± 0.45	1,984	0.40 ± 0.15	.001*
Total	2,240	3.79 ± 0.45	4,399	1.31 ± 0.15	.001*

*Highly significant

system within diencephalon, mesencephalon and probably rhombencephalon which has bilateral functional connections with the cerebral hemispheres." In keeping with this new term, Penfield and Jasper[6] formulated a system of classification which groups seizures into 3 main categories—localized, unlocalized, and centrencephalic—depending upon the site of origin of the epileptiform discharge within the brain. Insofar as the type of clinical seizure is often (but alas, not always) correlated with the type of electroencephalogram, the Penfield-Jasper system of classification has the potential advantage of singling out specific forms of epilepsy on the basis of both of these closely related variables. The genetic epileptologist's interest in this classification lies in the fact that some of the specific forms of epilepsy may turn out to be specific genetic forms of epilepsy.

Patients with centrencephalic epilepsy usually have petit mal and/or grand mal seizures. (Here we are using these terms in their French literal sense simply to grade the convulsions into minor and major without any other connotation.) Not infrequently, these patients also have a mixture of other forms of clinical epilepsy; however, by definition, they all have a characteristic electroencephalogram. The typical centrencephalic patients have a paroxysmal bilaterally synchronous 3-per-second wave-and-spike, and the atypical centrencephalic patients have a slight variant of this (see appendix).

In choosing, therefore, to consider centrencephalic epilepsy in our search for genetic factors, we do so primarily because this group can be identified on the single objective criterion of the electroencephalogram. Furthermore, the typical centrencephalic electroencephalogram is so characteristic that there is almost universal agreement among electroencephalographers as to its presence or absence from a particular record. It should be clear that whether centrencephalic epilepsy emanates from abnormal neuronal discharges in the higher brain stem or the cortex itself[7] or whether or not it is due to demonstrable, localized lesions[8] does not in any way alter the possibility that this form of epilepsy may be gene-controlled. We mention this because of the erroneous belief still held by many that, if pathology can be demonstrated, the trait cannot be genetic.

THE PROBANDS

Pursuing the general methods outlined in our first paper,[1] 211 probands with typical or atypical centrencephalic epilepsy were obtained from the Convulsive Disorders Clinic of the Neurology Service of The Montreal Children's Hospital. We repeat that these index patients have a history of recurrent petit mal and/or grand mal seizures, no obvious neuropathology to account for their seizures, and a centrencephalic electroencephalogram. To compare with these, 112 control probands were collected by examining the record of every twentieth admission to the hospital from which the centrencephalic probands were drawn. If the patient had no history of ever having had a convulsion, if the illness was not considered to be neuropathologic, and if the electroencephalogram was within normal or

TABLE 2
SEX DISTRIBUTION OF 211 CENTRENCEPHALIC AND 112 CONTROL PROBANDS

Sex	Centrencephalic			Control		
	Typical	*Atypical*	*Total*	*Normal*	*Borderline*	*Total*
Girls	42	66	108	30	9	39
Boys	39	64	103	56	17	73
Total	81	130	211	86	26	112

borderline normal limits, the patient was accepted as a control proband.

The ratio of boys to girls (103 ♂ ♂ : 108 ♀ ♀) among the centrencephalic patients is not significantly different from equality. The sex ratio among the control probands (73 ♂ ♂ : 39 ♀ ♀), although significantly different from the 1 : 1 ratio, is not significantly different from that found for the over-all hospital population[1] (Table 2). At this point, 2 observations may be made: [1] the control sample is representative, at least as far as sex ratio is concerned, of the hospital population and [2] centrencephalic epilepsy is equally prevalent among boys and girls and is not, therefore, one of the conditions that accounts for more boys than girls being admitted to this particular hospital.

The centrencephalic and control probands have been compared for a number of things, including parental age, ethnic origin, socioeconomic status, sibship size, and parity. For none of these was any significant difference demonstrable. Since birth order is often stated to be a factor in epilepsy, our findings for parity are presented in Table 3 and will be discussed briefly.

If first born are more subject to birth trauma, one would expect primogeniture to be one of the factors in focal epilepsy. However, the question here is whether it is a factor in epileptic patients with no demonstrable cerebral injury. Nielsen and Butler[9] have suggested that "birth primacy" is a cause of idiopathic epilepsy. On the other hand, Orr and Risch[10] have suggested that "epilepsy occurred more frequently in people approaching the end of the line of birth rather than in those holding the position of first born."

In this study, the prevalence of first born among the centrencephalic patients (39.34%) is not significantly different from that found among the controls (36.61%). Furthermore, the entire distribution of birth orders in the 2 groups is not significantly different ($P = .10$). There is therefore no evidence from these data that birth order is an etiologic factor in centrencephalic epilepsy.

CONVULSIONS IN NEAR RELATIVES

Information regarding age, medical history, cause of death, and, particularly, convulsive disorders was obtained for 7,377 centrencephalic and 4,026 control relatives. The pre-

TABLE 3
PARITY OF CENTRENCEPHALIC AND CONTROL PROBANDS

Birth order	*Centrencephalic*		*Control*		x^2
	Number	*Per cent*	*Number*	*Per cent*	
1	83	39.34	41	36.61	.14
2	56	26.54	18	16.07	3.50
3	38	18.01	23	20.54	.25
4	15	7.11	9	8.04	.09
5	7	3.32	8	7.14	2.31
6	7	3.32	5	4.46	.26
7 to 13	5	2.36	8	7.14	4.13
Total	211	100.00	112	100.00	10.68

$x^2 = 10.68$ degrees of freedom = 6 $P = .10$ (not significant)

TABLE 4
PREVALENCE OF INDIVIDUALS WITH CONVULSIONS AMONG THE NEAR RELATIVES OF CENTRENCEPHALIC AND CONTROL PROBANDS

Relationship to proband	*Centrencephalic*		*Control*		*P*
	Number	*% affected*	*Number*	*% affected*	
Parents	422	13.51 ± 1.66	224	1.34 ± 0.77	.001*
Siblings	519	12.72 ± 1.46	322	4.66 ± 1.17	.001*
Aunts and uncles	2,167	4.20 ± 0.43	1,213	3.13 ± 0.50	.050
Grandparents	844	2.61 ± 0.55	448	0.67 ± 0.39	.005*
Cousins	3,425	1.46 ± 0.20	1,819	0.66 ± 0.19	.005*
Total	7,377	3.88 ± 0.22	4,026	1.76 ± 0.21	.001*

*Highly significant

valence of individuals with a history of one or more convulsions among the near relatives of the centrencephalic and control probands is compared in Table 4. Because no sex differences were found and because affected individuals were equally distributed among maternal and paternal relatives, the 20 classes of relatives[1] have been combined into 5 classes: Parents, Siblings, Aunts and Uncles, Grandparents, and Cousins. It will be noted that, with the exception of the class Aunts and Uncles, the prevalence of affected individuals in the centrencephalic group is significantly greater for each class of relative than in the control group. (Although it is usual to accept $P = .05$ as the level of statistical significance, for these studies, because we are dealing with a one-tailed distribution, $P = .02$ is accepted as significant and $P = .001$ as highly significant.)

As in the case of our base-line studies,[1] we again find that the data clearly demonstrate a familial distribution for convulsions, for, as the genetic distance between the relative studied and the proband increases, the prevalence of affected individuals decreases (from approximately 13% in the parents and siblings to approximately 2% in the grandparents and cousins) in the case of the centrencephalic group but tends to fluctuate within narrower limits around 2% for each class of relative in the control group. When all the relatives are considered together, the prevalence for the centrencephalic group ($3.88 \pm 0.22\%$) is 2.2 times greater and significantly higher ($P = < .001$) than for the control group ($1.76 \pm 0.21\%$).

It has been mentioned above that, on the basis of the electroencephalogram, the centrencephalic probands were divided into typical and atypical. In order to see if the distribution of near relatives with convulsions is the same for the typical and atypical centrencephalics, the 2 subgroups were considered separately and are compared in Table 5. It is quite evident from this comparison that the 2 subgroups are not different, at least with respect to prevalence of near relatives with a

TABLE 5
PREVALENCE OF INDIVIDUALS WITH CONVULSIONS AMONG THE NEAR RELATIVES OF TYPICAL AND ATYPICAL CENTRENCEPHALIC PROBANDS

Relationship to proband	*Typical*		*Atypical*		*P*
	Number	*% affected*	*Number*	*% affected*	
Parents	162	11.73 ± 2.53	260	14.62 ± 2.19	.40
Siblings	200	13.50 ± 2.42	319	12.23 ± 1.83	.70
Aunts and uncles	790	4.18 ± 0.71	1,377	4.21 ± 0.54	.90
Grandparents	324	2.78 ± 0.91	520	2.50 ± 0.68	.90
Cousins	1,229	1.95 ± 0.39	2,196	1.18 ± 0.23	.10
Total	2,705	2.14 ± 0.38	4,672	3.72 ± 0.28	.40

TABLE 6

PREVALENCE OF INDIVIDUALS WITH CONVULSIONS AMONG THE NEAR RELATIVES OF FEMALE AND MALE CENTRENCEPHALIC PROBANDS

Relationship to proband	*Female*		*Male*		*P*
	Number	*% affected*	*Number*	*% affected*	
Parents	216	13.43 ± 2.32	206	13.59 ± 2.39	.90
Siblings	256	14.45 ± 2.20	263	11.03 ± 1.93	.30
Aunts and uncles	1,177	4.25 ± 0.59	990	4.14 ± 0.63	.90
Grandparents	432	2.31 ± 0.72	412	2.91 ± 0.83	.60
Cousins	1,984	1.51 ± 0.27	1,441	1.39 ± 0.31	.80
Total	4,065	3.84 ± 0.30	3,312	3.93 ± 0.34	.90

history of convulsions. The pooling of typical and atypical centrencephalics, therefore, appears justifiable.

Several investigators, including Lennox[4] and Ounsted,[11] have reported a higher prevalence of affected near relatives when the proband is female than when the proband is male. In order to test this, the near relatives of female probands have been considered separately from those of male probands. The results, as compared in Table 6, show no suggestion whatsoever of a higher prevalence of affected near relatives of female probands.

ELECTROENCEPHALOGRAPHIC ABNORMALITIES

In view of the fact that the centrencephalic probands were ascertained primarily on the basis of a highly specific type of epileptiform electroencephalogram, it was deemed desirable to study the electroencephalograms of the parents and siblings. Consequently, an attempt has been made to obtain an electroencephalogram for all available parents and siblings of both the centrencephalic and control probands. Only 1 electroencephalogram is taken for each parent and each sibling. (In a few cases, a repeat electroencephalogram was necessary because the first was considered to be technically inadequate. If repeat electroencephalograms are done on parents or siblings for any other reason, they are not considered in the present analyses.) In addition to the resting record, a tracing is obtained during hyperventilation and photic stimulation. All records (probands', parents', and siblings') are reviewed by 1 electroencephalographer (K.M.) and are coded

TABLE 7

PREVALENCE OF ELECTROENCEPHALOGRAPHIC ABNORMALITIES IN PARENTS OF CENTRENCEPHALIC AND CONTROL PROBANDS

Electroencephalographic abnormality†	*Centrencephalic N = 195*	*Control N = 84*	*P*
Normal	71.79 ± 3.22	78.57 ± 4.48	.100
Borderline normal	14.87 ± 2.55	7.14 ± 2.18	.025
Typical centrencephalic	1.03 ± 0.72	0.00 ± 0.84	.200
Atypical centrencephalic	6.67 ± 1.79	2.38 ± 1.66	.050
Theta rhythms	0.00 ± 0.36	0.00 ± 0.84	.999
Multiple diffuse	2.56 ± 1.13	4.76 ± 2.32	.200
Focal	2.56 ± 1.13	5.95 ± 2.58	.150
Others	0.51 ± 0.51	1.19 ± 1.18	.300
Normal plus borderline	86.67 ± 2.43	85.71 ± 3.82	.400
Total abnormal	13.33 = 2.43	14.29 ± 3.82	.400
Total centrencephalic	7.69 ± 1.91	2.38 ± 1.66	.025
Total epileptiform	9.23 ± 2.07	5.95 ± 2.58	.150

†See Appendix

according to the classification referred to in the appendix. Very briefly, the main classifications are Normal, Borderline, and Abnormal. The Abnormal is further divided into Centrencephalic, Nonspecific Bilateral Theta Rhythms, Unlocalized Multiple Diffuse Dysrhythmias, Focal Dysrhythmias, and Others. The Centrencephalic is still further divided into Typical and Atypical, depending upon whether the typical 3-per-second wave-and-spike or some variant of this is present.

In Table 7, the electroencephalographic findings in 195 parents of centrencephalic and 84 parents of control probands are listed and compared. On the whole, no startling differences were found, for in both groups the total number of cerebral dysrhythmias was approximately 14% and the total number of Normal plus Borderline, approximately 86%. The only thing of note, and of particular interest to us here, is the fact that 15 of the 195 parents of the centrencephalic group had themselves a centrencephalic type of electroencephalogram, whereas only 2 of the 84 parents of the control group had such an electroencephalogram. The 2 percentages, 7.69% and 2.38%, are significant at the $P = .025$ level. It is possible that, with larger numbers of parents tested, some real differences may be proved; for example, the number of parents with epileptiform electroencephalograms in the centrencephalic group (9.23%) is substantially higher than that in the control group (5.95%). However, all that can be said at the present is that this difference is not a statistically significant one for $P = .15$.

Before leaving the seemingly negative electroencephalographic findings for the parents of centrencephalic and control probands, one should recall that centrencephalic epilepsy and the centrencephalic type of electroencephalogram is age-specific and tends to "burn itself out" as the patient reaches his late teens. Therefore, since only 1 electroencephalogram of parents at the average age of 30 years was taken, it is not surprising that relatively few centrencephalic electroencephalograms were recorded. It is important to know whether more of the parents of the centrencephalic group had centrencephalic electroencephalograms at an earlier age. Unfortunately, no such electroencephalographic records exist, and a direct answer to this question cannot be given; however, an indirect answer will be suggested later on when we compare the age distribution of the parental and sibling records.

The electroencephalographic data for 223 siblings of centrencephalic and 103 siblings of control probands are presented in Table 8. Some striking contrasts appear, for in the centrencephalic group one finds approximately twice as many siblings with some form of elec-

TABLE 8

PREVALENCE OF ELECTROENCEPHALOGRAPHIC ABNORMALITIES IN SIBLINGS OF CENTRENCEPHALIC AND CONTROL PROBANDS

Electroencephalographic abnormality†	*Centrencephalic* $N = 223$	*Control* $N = 103$	*P*
Normal	29.60 ± 3.06	45.63 ± 4.91	.005*
Borderline normal	17.04 ± 2.52	26.21 ± 4.33	.050
Typical centrencephalic	2.24 ± 0.99	0.00 ± 0.69	.100
Atypical centrencephalic	34.53 ± 3.18	8.74 ± 2.78	.001*
Theta rhythms	2.24 ± 0.99	1.94 ± 1.36	.450
Multiple diffuse	8.07 ± 1.82	10.68 ± 3.04	.250
Focal	4.04 ± 1.32	4.85 ± 2.12	.400
Others	2.24 ± 0.99	1.94 ± 1.36	.450
Normal plus borderline	46.64 ± 3.34	71.84 ± 4.43	.001*
Total abnormal	53.36 ± 3.34	28.16 ± 4.43	.001*
Total centrencephalic	36.77 ± 3.23	8.74 ± 2.78	.001*
Total epileptiform	46.19 ± 3.34	15.53 ± 3.57	.001*

†See Appendix
*Highly significant

TABLE 9
AGE DISTRIBUTION OF SIBLINGS AND PARENTS WITH CENTRENCEPHALIC ELECTROENCEPHALOGRAMS

Age in years	Siblings			Parents			Totals		
	Number	Total	%	Number	Total	%	Number	Total	%
½ to 4½	15	59	25.4				15	59	25.4
4½ to 8½	35	79	44.3				35	79	44.3
8½ to 12½	22	49	44.9				22	49	44.9
12½ to 16½	8	18	44.4				8	18	44.4
16½ to 20½	2	9	22.2				2	9	22.2
20½ to 24½	0	7	—	2	10	20.0	2	17	11.8
24½ to 28½	0	1	—	2	25	8.0	2	26	7.7
28½ to 32½	0	1	—	3	41	7.3	3	42	7.1
32½ to 36½				5	44	11.4	5	44	11.4
36½ to 40½				2	35	5.7	2	35	5.7
40½ to 44½				1	24	4.2	1	24	4.2
44½ to 48½				0	7	—	0	7	—
48½ to 52½				0	4	—	0	4	—
52½ to 56½				0	4	—	0	4	—
56½ to 60½				—	—	—	0	1	—
60½ to 64½				0	1	—	—	—	—
Total	82	223	36.8	15	195	7.7	97	418	23.2

troencephalographic abnormality (53.36%) as in the control group (28.16%). When only epileptiform dysrhythmias are considered, the number of siblings with such an abnormality in the centrencephalic group (46.19%) is 3 times as high as in the control group (15.53%). It is of great import that this difference is due almost entirely to the higher number of siblings with centrencephalic electroencephalograms in the centrencephalic group (36.77%) than in the control group (8.74%).

THE ANSWER (?)

Since it was found that approximately 37% of the siblings of probands with centrencephalic epilepsy had themselves a centrencephalic type of electroencephalogram, irrespective of whether they also had clinical seizures, it became of interest to see what, if any, was the genetic interpretation. (Incidentally, the 9 of the 103 siblings of the control group that had a centrencephalic type of electroencephalogram were confined to 5 sibships only—1 with 3 affected, 2 with 2 affected each, and 2 with 1 affected each. The data from the control group, therefore, also suggest a tendency for a familial congregation.)

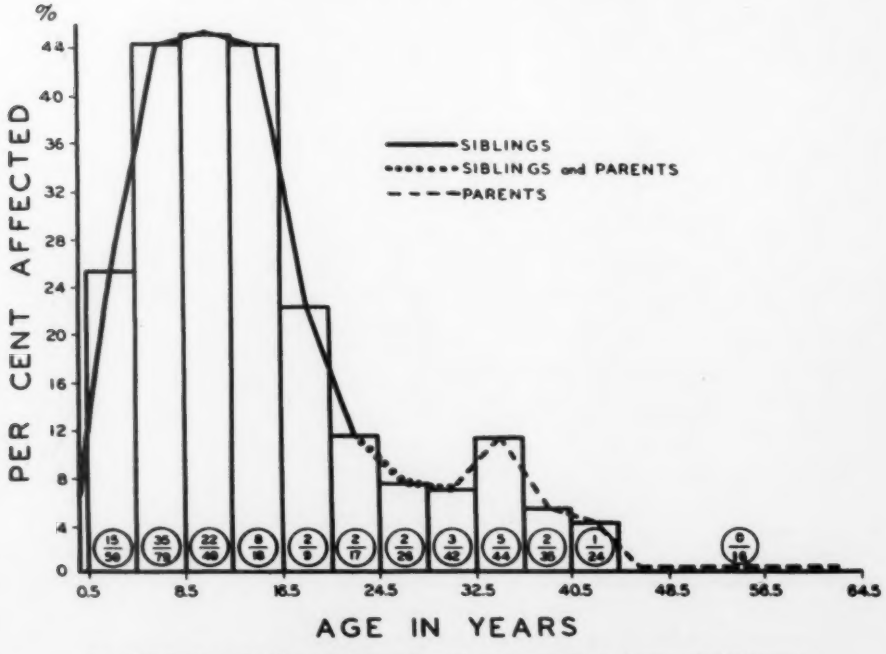
If one discounts for the moment biases due to method of ascertainment—a thorny subject which will be discussed elsewhere—the 37% over-all risk for siblings is significantly higher than the 25% risk expected on the basis of a simple autosomal recessive gene but does fit the hypothesis of a dominant gene with reduced penetrance, where something less than 50% is expected. However, if this is the case and we are indeed dealing with a dominant gene with 26% lack of penetrance, then, barring variability in the age of onset, 37% of the parents should also show the type of electroencephalogram in question. Only 7.69% did! This apparent discrepancy tempts one to discard the irregular dominant gene hypothesis until it is recalled that the trait that is being sought—the paroxysmal bilaterally synchronous 3-per-second wave-and-spike—tends to disappear in the late teens and is almost unknown in adulthood.

In order to analyze the effect of age on the presence or absence of the centrencephalic type of electroencephalogram, the electroencephalograms of the parents and siblings were grouped according to the age of the individual at the time that the record was obtained. These

data are presented numerically in Table 9 and graphically in the figure. It is clearly evident that age has an important bearing on whether the electroencephalographic trait will be present. Between the ages of 4½ and 16½ years, approximately 45% of siblings tested had the electroencephalographic trait. After 16½ years, there is a sharp decline, so that only 1 (42 years old) of the 40 parents tested after the age of 40½ years had the electroencephalographic trait. That the trait is not fully developed at birth is evident from the fact that, of 16 siblings tested before the age of 2½ years, only 1 (11 months old), or 6.3%, had the electroencephalographic trait. It is of particular interest to point out that the break in the curve between the point where the sibling data leave off (22.2% for ages 16½ to 20½ years) and the point where the parent data begin (11.4% for ages 32½ to 36½ years) is made quite continuous when the combined sibling-parent data for the age range 20½ to 32½ years are introduced. (The peak at age 34½ years is, of course, not a significant one, for 5/44 is not statistically different from either 3/42 or 2/35.)

It would appear, therefore, that, if due allowance is given to the variability of age at onset of the centrencephalic type of electroencephalogram and also to its tendency to disappear in later years, the data are compatible with the hypothesis that an autosomal dominant gene is responsible for the centrencephalic electroencephalogram. Of 40 siblings between the ages of 4½ and 7½ years tested, 20, or exactly 50%, had the electroencephalographic trait. Admittedly, this is a selected age range which does not appear in the table or histogram of four-year intervals. However, the fact that some age groups can reach the theoretic 50% expectation suggests that the gene may be fully penetrant provided its effect is looked for at the optimum age.

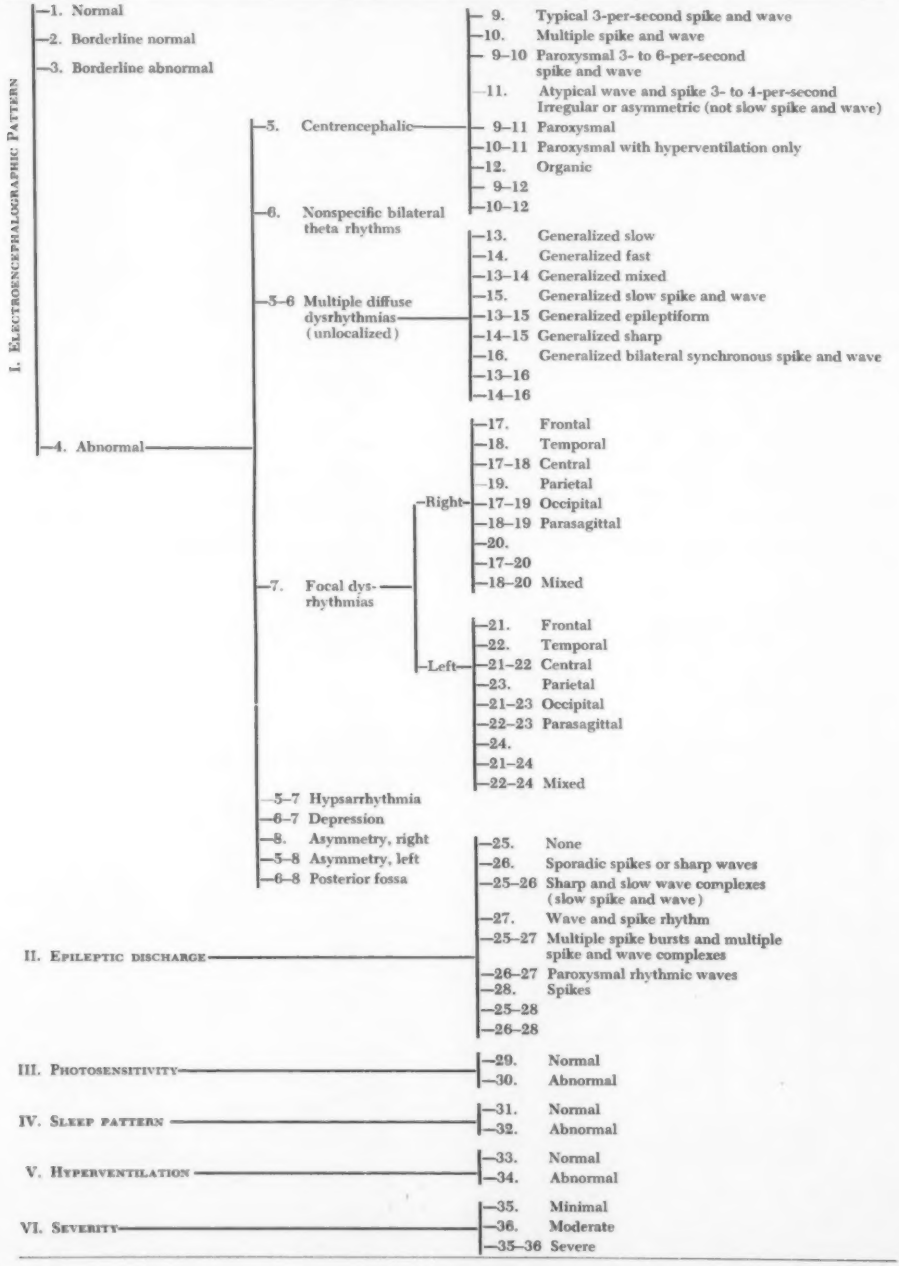
The reader may well ask what is the correlation between a history of clinical seizures and the presence of a centrencephalic electroencephalogram. This, of course, is a most per-



Age distribution of siblings and parents with centrencephalic electroencephalograms

APPENDIX

ELECTROENCEPHALOGRAPHIC CLASSIFICATION



tinent question, and we propose to discuss it in some detail elsewhere. Suffice it to say here that, since only 13% of the siblings have a history of convulsions, the 37% of siblings with the electroencephalographic trait cannot all be affected with convulsions. What possible factors may be operating to precipitate clinical seizures in a child with a centrencephalic electroencephalogram and what the significance of this is in genetic counselling will also be considered in a subsequent paper.

CONCLUSION

The chief conclusion derived from this study is that the centrencephalic type of electroencephalogram is the expression of an autosomal dominant gene, with the unusual characteristic of a very low penetrance at birth, which rises rapidly to nearly complete penetrance for ages 4½ to 16½ years and declines gradually to almost no penetrance after the age of 40½ years.

In the first part of this series of papers, we expressed our sincere thanks to all those individuals and institutions "who in no less than a thousand and one ways have contributed directly to our study" of convulsive disorders. Now we wish to acknowledge with extreme gratitude the contributions of the Director of the Department of Medical Genetics where the field work of this study was conducted. Dr. F. Clarke Fraser not only "directed" but indeed inspired this particular aspect of the study by his continued insistence that we attempt to delineate specific forms of epilepsy. To him we express our sincere appreciation.

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Ultraviolet absorption by human spinal fluid in health and disease

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SEVERAL AUTHORS have shown that the spinal fluid has the property of absorbing transmitted light, including ultraviolet light, to a variable degree. This absorption of ultraviolet light has been studied in health and disease. However, the reported results are inconsistent; the absorption curves reported by different authors for normal spinal fluid are not identical. The same lack of uniformity exists among curves obtained with spinal fluid from patients with identical diagnoses studied by different investigators. Examples of these discrepancies in the literature are shown in Figure 1.

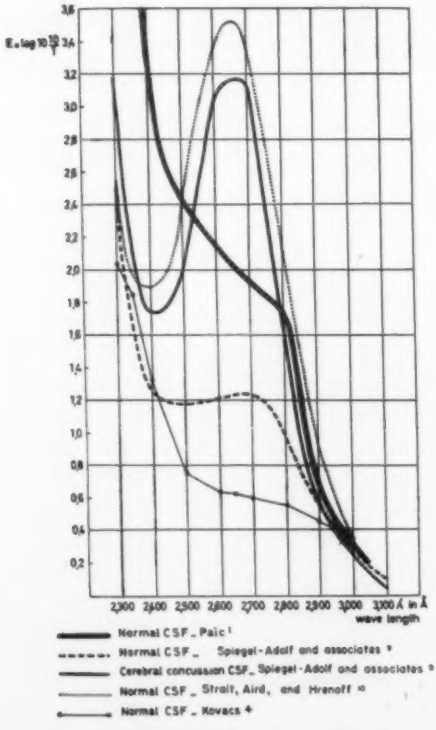

Fig. 1. Discrepancies among absorption curves reported by various authors

Conflicting views have been expressed concerning the chemical compounds responsible for the ultraviolet absorption of the spinal fluid. It has been attributed to proteins,[1–3] to products resulting from the degradation of nucleic acids,[4–9] and to ascorbic acid.[10]

The present work was undertaken in order to elucidate the significance of the ultraviolet absorption curves with respect to the chemical composition of normal and abnormal spinal fluids and to provide an explanation for the divergent results obtained by different investigators using the spectrophotometric method of study.

METHODS

Measurements. All measurements were made at 25° C. in a Beckman DU spectrophotometer with a constant temperature attachment. Before measurement, the spinal fluid was diluted with an equal volume of redistilled water or isotonic saline. The former was used as a blank.

Since preliminary experiments showed a great lability of the ultraviolet absorption at 25° C. resulting in a rapid decrease with time in the range of maximal absorption, 2,650 Å (Fig. 2), the total absorption of the spinal

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fluid was measured immediately after lumbar puncture. The samples were kept at 0° C. during the short period between the puncture and the actual measurement in the laboratory. This first measurement, done as quickly as possible, gave a value called "total absorption." A second sample of the same spinal fluid was left for four hours at room temperature (18 to 22° C.) and the absorption again measured. The absorption at that time was found to be greatly decreased, and the difference between the first measurement and the measurement carried out after incubation at room temperature for four hours was called the "spontaneous decrease of absorption" because, after that time, absorption remained practically constant. The spontaneous decrease of absorption of spinal fluid at several wave lengths in the ultraviolet range is shown in Figure 2, and the values for total absorption of different samples of spinal fluid are given in Tables 1 through 3. The rate of the decrease of absorption was greater at alkaline *p*H's and much slower at acid *p*H's.

In order to evaluate the contribution from the protein moiety of the spinal fluid to the intensity of absorption, a duplicate curve was obtained on the protein-free filtrate of each sample. This was prepared by salting out the spinal fluid with saturated ammonium sulphate solution and filtering. The difference between total absorption and absorption of the protein-free filtrate represented the "absorption due to proteins" (Table 1).

In order to determine the fraction of the total absorption not due to the spontaneous decrease on standing or to the presence of proteins, absorption was measured after the following processing: Spinal fluid was adjusted to *p*H 12 by the addition of NaOH N/10. After thirty minutes, the spinal fluid was salted out with saturated ammonium sulphate and filtered. The absorption of the filtrate was called the "residual absorption," and its values, at the wave length of maximal absorption, are given in Table 1 for 15 different samples of spinal fluid.

Determinations of ascorbic acid as well as of its oxidized derivatives—dehydroascorbic acid and gulonic acid—were done by the chemical methods of Roe and Kuether[11] using 2, 4-dinitrophenylhydrazine.

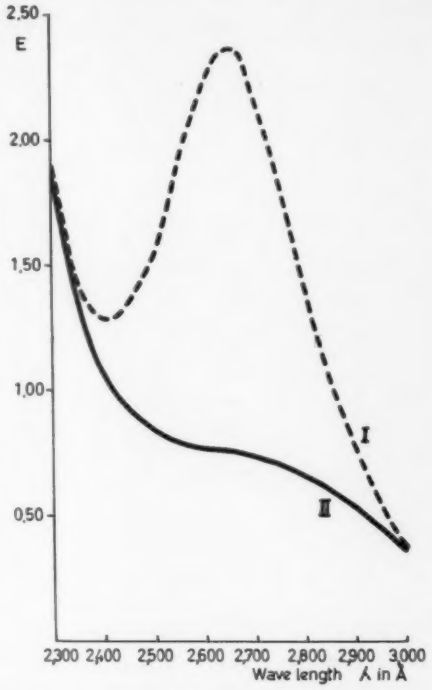

Fig. 2. Effect of incubation at room temperature on ultraviolet absorption of spinal fluid. Curve I=absorption immediately after lumbar puncture. Curve II=absorption after four hours' incubation at room temperature

Patients. Spinal fluids from 75 patients of either a neurosurgical or a cancer center were examined. In 32, clinical and laboratory examinations demonstrated the absence of neurologic diseases. Absorption was measured on fresh samples in all cases. Tables 2 and 3 show the wave lengths of maximal and minimal absorption, as well as the value of total absorption at the wave length of maximal absorption. In 15 cases, fractionation of the spinal fluids, as outlined above, was done and the partial absorptions measured (Table 1 and Fig. 3).

RESULTS

Total absorption. All the 75 spinal fluids studied in this work showed selective absorption in the ultraviolet range of the spectrum.

TABLE 1

FRACTIONATION OF 15 DIFFERENT SAMPLES OF SPINAL FLUID

Diagnosis	*Total absorption at 2,650 A* *a*	*Absorption due to ascorbic acid* *b=a−(c+d)*	*Absorption due to protein* *c*	*Residual absorption* *d*
Tuberculoma	1.600	.720	.280	.600
Disseminated sclerosis	1.800	1.380	.060	.360
Jacksonian epilepsy	2.940	2.500	.020	.420
Temporal glioma	2.640	1.640	.400	.600
Cerebral metastasis	1.360	.120	.220	1.020
Epilepsy	1.800	1.220	.140	.440
Retrobulbar neuritis	3.360	2.620	.140	.600
Parasagittal glioma	3.440	.440	2.140	.860
Cerebral metastasis	2.000	.440	.800	.760
Mammary carcinoma	4.120	3.620	.020	.480
Hodgkin's disease	3.800	3.240	.080	.480
Disseminated sclerosis	3.000	2.340	.100	.560
Carcinoma of esophagus	1.080	.280	.080	.720
Epilepsy	1.640	.600	.420	.620
Medullary compression	5.120	.400	2.640	2.080

TABLE 2

PATIENTS WITH DISEASES OF THE NERVOUS SYSTEM

Number	*Record*	*Age*	*Sex*	*Diagnosis*	*Range of maximal absorption*	*Range of minimal absorption*	*Total absorption at 2,650 A*
1*	JP	50	M	Alcoholic polyneuritis	2,760-2,780	2,550	0.92
2	SJ	70	M	Cerebral metastasis; suspected carcinoma of kidney	2,800	2,600	1.36
3	MA	6	M	Right cerebellar syndrome of unknown origin	2,650	2,450	1.40
4*	VJ	28	F	Diffuse gliomatosis; right hemiparesis, hemianopsia, aphasia	2,640-2,680	2,500-2,550	1.44
5*	BM	62	M	Pick's disease	2,670-2,690	2,550	1.44
6	MH	52	F	Cerebral metastasis, cutaneous nevo-carcinoma	2,750-2,800	2,550-2,600	1.46
7	SG	42	M	Suspected lesion of pontocerebellar region; angiography shows functional anomalies of posterior cerebellar veins	2,650	2,500	1.48
8	VH	63	M	Carcinoma of lung; cerebral ictus 2 years before spinal puncture; EEG: persistent signs of cerebral dysfunction	2,650	2,500	1.52
9*	DL	54	F	Cerebral vascular accident due to aneurysm; right hemiplegia and aphasia	2,650-2,660	2,500	1.58
10	MG	55	M	Frontoparietal tuberculoma; jacksonian crises	2,650	2,550	1.60
11*	ZF	46	M	Cerebral metastasis of ocular melanosarcoma	2,740-2,780	2,550-2,600	1.68
12	BH		M	Epilepsy	2,650	2,500	1.68
13	VJ	49	M	Temporal epilepsy	2,640-2,700	2,500-2,550	1.70
14	DS	20	F	Epilepsy	2,650	2,450-2,500	1.80
15	SG	21	M	Postconcussion syndrome, 8 months after accident	2,650	2,450	1.80
16	BM	49	F	Mammary carcinoma with EEG evidence of cerebral metastasis	2,700	2,500	1.90
17*	JF	69	M	Cerebrovascular accident, 3 months previously; right hemiparesis	2,640-2,650	2,550-2,600	2.00
18	LM	73	F	Cerebral metastasis of bronchial carcinoma	2,650	2,550	2.00

TABLE 2 (*continued*)

Number	*Record*	*Age*	*Sex*	*Diagnosis*	*Range of maximal absorption*	*Range of minimal absorption*	*Total absorption at 2,650 Å*
19	MP	35	M	Left intracerebellar hematoma	2,700	2,550-2,600	2.10
20*	LA	39	M	Epilepsy; normal encephalography	2,630-2,670	2,500	2.12
21	LV	64	M	Generalized reticulosarcoma with involvement of spinal meninges	2,650	2,500	2.32
22	CB	35	F	Cerebral tumor of probable meningeal origin	2,650	2,500	2.45
23	SE	47	M	Benign transient cerebral hypertension (pseudotumor cerebri)	2,650-2,700	2,450	2.46
24*	VM	55	F	Adenocarcinoma of uterus with polyneuritis	2,650-2,660	2,500	2.48
25*	CJ	43	F	Postconcussion syndrome; lumbar puncture 8 months after trauma	2,640-2,660	2,450	2.52
26*	KM	61	F	Vascular encephalopathy	2,650-2,670	2,450	2.60
27	MR	31	M	Acromegaly; right oculomotor palsy	2,650	2,450	2.62
28	VF	59	M	Right hemiplegia and aphasia; glioma of the temporal lobe	2,650	2,500	2.64
29	CML	34	F	Benign transient cerebral hypertension	2,650	2,400	2.68
30*	EF	43	M	Benign transient cerebral hypertension	2,630-2,660	2,450	2.74
31	PM	42	F	Pernicious anemia with combined sclerosis	2,650	2,450	2.78
32	VA	63	M	Diskal hernia (L3-L4 / L4-L5)	2,650	2,450	2.90
33	TJ	51	F	Amyotrophic lateral sclerosis	2,650	2,500	2.92
34	FE	20	M	Right jacksonian epilepsy	2,650	2,500	2.94
35	R			Disseminated sclerosis	2,650		3.00
36	NF	8	M	Encephalitis; right hemiplegia, aphasia	2,650	2,450	3.28
37	FG	50	M	Bilateral facial palsy due to herpes zoster; syphilis	2,650	2,450	3.30
38	DF		F	Retrobulbar neuritis	2,650	2,400	3.36
39	DA	43	M	Postconcussion syndrome	2,650	2,450	3.36
40*	CP	36	M	Diskal hernia	2,650-2,660	2,450	3.40
41	DA	45	M	Parasagittal glioma; jacksonian crises	2,650	2,450	3.44
42	FA	50	M	In 1955, surgical removal of a frontal glioma; in 1957, marked cerebral atrophy	2,650	2,450	4.44
43	DM		M	Compression of sacral roots by metastasis of carcinoma of unknown primary site; CSF protein: 1.9 gm. per liter	2,650		5.12

*The absorption peak has been determined by 10-Å steps for these samples.

Maximal absorption occurred between 2,650 and 2,680 Å (Tables 2 and 3).

The magnitude of the absorption varied considerably from one individual to another. The lowest and highest total absorptions recorded at 2,650 Å were, respectively, E : 0.86 and E : 5.12 (Tables 2 and 3). In the same patient, total absorption was variable from day to day and did not represent an individual characteristic.

Role of ascorbic acid in absorption curve of spinal fluid. As indicated above, spinal fluid showed a spontaneous decrease in absorption on incubation at room temperature (20 to 25° C.), resulting in the conversion of curves with an initial selective absorption band at 2,650 Å into curves with no definite peak or with a small peak at 2,800 Å (Fig. 2). On the other hand, we observed that solutions of pure ascorbic acid showed a similar transformation. This is due to spontaneous oxidation of ascorbic acid into dehydroascorbic acid; the latter compound does not absorb light in the ultraviolet range. The fact that ascorbic acid present in spinal fluid is responsible for part of the absorption curve of this fluid was confirmed by the effect of alkalinization on this curve: at *p*H 12, absorption of ultraviolet light decreased sharply, the difference sometimes amounting to as much as

TABLE 3
PATIENTS WITHOUT DISEASE OF THE NERVOUS SYSTEM

Number	*Record*	*Age*	*Sex*	*Diagnosis*	*Range of maximal absorption*	*Range of minimal absorption*	*Total absorption at 2,650 Å*
1	DF	51	M	Generalized carcinomatosis; pulmonary or renal origin	2,650	2,600	0.86
2	WG	63	M	Epithelioma of gum	2,750	2,600	0.88
3	MP	54	M	Deforming spondylosis	2,750-2,800	2,550-2,600	0.94
4	MJ	5	M	Unverified diagnosis of cerebral tumor	2,650	2,500-2,550	1.07
5	DG	57	M	Maxillar adamantinoma	2,650		1.08
6*	BA	53	M	Psychogenic pains	2,650-2,610	2,550	1.08
7*	BE	70	M	Nontoxic goiter	2,670-2,700	2,550	1.12
8*	RF	67	F	Rabdomyosarcoma	2,660-2,710	2,550	1.14
9*	DA	58	F	Lymphosarcoma	2,670-2,740	2,550	1.20
10	MM	20	M	Mediastinal tumor of unknown nature; radiosensitive	2,650-2,700	2,500	1.32
11*	CM	30	M	Lumbosacral spondylarthrosis	2,660-2,680	2,500	1.33
12*	LA	40	M	Bronchial carcinoma; under radiotherapy	2,660-2,720	2,500-2,550	1.34
13*	DA	58	M	Epithelioma of tongue, involving pharynx; x-ray treatment before	2,640-2,660	2,500-2,550	1.55
14*	PV	45	F	Hodgkin's disease	2,640-2,690	2,500	1.68
15*	DL	63	M	Carcinoma of esophagus	2,640-2,660	2,500	1.78
16*	CA	46	M	Epithelioma of tongue	2,640-2,650	2,500	1.80
17	PJ	21	M	Ophthalmic migraine; no arteriographic anomaly	2,650	2,450	1.84
18	FC	70	M	Inoperable bronchial carcinoma; under x-ray treatment	2,650	2,500	1.88
19*	LC	62	M	Bronchial carcinoma; under x-ray treatment	2,640-2,670	2,450-2,500	2.16
20	BB	54	M	Reticulosarcoma	2,650	2,450	2.44
21*	VOJ	65	M	Bronchial carcinoma under cyclotherapy; spinocellular carcinoma of anal margin	2,660-2,700	2,450	2.76
22*	WR	46	F	Epithelioma of gum	2,670	2,450-2,500	2.84
23	MF	53	M	Hodgkin's disease; terminal coma	No definite peak		2.90
24	RE	34	M	Tinnitus	2,650	2,450	2.98
25*	GM	45	F	Nontoxic goiter	2,640-2,670	2,450	3.06
26*	LM	34	F	Tinnitus	2,650-2,670	2,450	3.28
27*	VAJ	64	F	Reticulosarcoma under x-ray therapy	2,640-2,650	2,400	3.28
28*	RR	62	M	Epithelioma of gum	2,640-2,660	2,400	3.44
29*	VN	46	F	Carcinoma of uterine cervix	2,640	2,400-2,450	3.50
30*	LW	40	M	Chronic myeloid leukemia	2,650	2,400	3.78
31	AJ	44	F	Hodgkin's disease	2,650		3.80
32	MM	79	F	Mammary carcinoma under x-ray treatment	2,650		4.12

*The absorption peak has been determined by 10-Å steps for these samples.

nine-tenths of the initial value at 2,650 Å. This decrease occurred in a few minutes, confirming the observations of Strait, Aird, and Hrenoff.[10] It was found that the absorption spectrum of this fraction of the spinal fluid was very dependent on *p*H, as shown by the fact that a shift of the maximal absorption to shorter wave lengths was observed concomitantly with acidification. This was true for spinal fluid as well as for water solutions of pure ascorbic acid. In order to test the hypothesis that the spontaneous decrease of absorption of the spinal fluid is due to ascorbic acid, the chemical determinations of ascorbic acid and its derivatives in the spinal fluid were done by the standard method of Roe and Kuether.[11] The amounts—ranging from 0.4 to 3.8 mg. per cent—gave an absorption in ultraviolet light quantitatively identical with the spontaneous decrease of absorption at room temperature and the decrease due to addition of alkali within the experimental error. These results for 12 different samples of spinal fluid are tabulated in Table 4. The difference in intensity of absorption at 2,650 Å between the total absorption and the absorp-

tion due to protein and unidentified products thus accounts for the ascorbic acid (Table 1).

Role of proteins in absorption curve of spinal fluid. The difference in intensity of absorption at 2,650 Å before and after salting out with saturated ammonium sulphate represents the part played by protein absorption at this wave length.

Part of absorption due to unknown factors. The spinal fluid, treated to *p*H 12 with NaOH N/10 salted out with saturated ammonium sulphate and filtered, showed a "residual absorption" independent of the presence of ascorbic acid and proteins (Table 1). This fraction is thus stable at alkaline *p*H and not precipitable with saturated ammonium sulphate; it did not change with time.

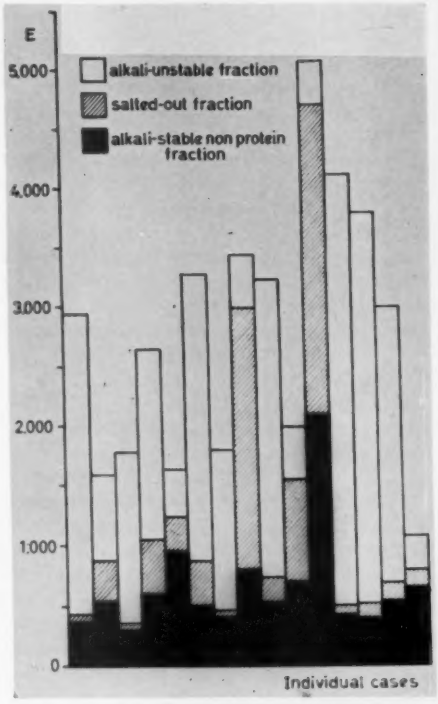

Fig. 3. Fractionation of 15 cerebrospinal fluids according to method described in text

DISCUSSION

Our data show the following facts:

All the spinal fluids examined in this work showed a maximal absorption at or near 2,650 Å.

Furthermore, all the spinal fluids in the range from 2,300 to 3,000 Å showed only 1 maximal absorption band.

Finally, at least 3 fractions were found to be responsible for the absorption of the spinal fluid at 2,650 Å. The results indicate clearly the lack of correlation between the total ab-

TABLE 4
COMPARISON OF CHEMICAL DOSAGE OF VITAMIN C AND SPONTANEOUS DECREASE OF ABSORPTION

Diagnosis	*Sex*	*Age*	*Chemical dosage of vitamin C (mg. per cent)*	*Calculated absorption due to vitamin C*	*Spontaneous decrease of absorption*
Tuberculous meningitis	M	20	1.05	0.538	0.600
Vaccinal reaction	M	19	0.83	0.473	0.450
Trigeminal zona	M	33	0.92	0.524	0.500
Vaccinal reaction	M	19	1.15	0.655	0.700
Generalized bronchial carcinoma	M	50	0.45	0.256	0.284
Breast cancer, localized	F	72	1.70	0.965	1.020
Multiple myeloma	M	67	0.40	0.228	0.250
Temporal glioblastoma	M	20	1.00	0.570	0.505
Encephalitis	M	22	1.17	0.666	0.702
Disseminated sclerosis	M	33	0.58	0.330	0.320
Thyroid cancer with osseous metastasis	M	64	2.80	1.596	1.235
Anemia	M	51	0.58	0.330	0.300

sorption at 2,650 Å and any 1 of the partial absorptions (Fig. 3). Of these, 2 could be defined; they corresponded respectively to ascorbic acid and to proteins. Attempts at determining the chemical nature of the third fraction have not been made by us, but we think that amino acids (phenylalanin, tryptophan) and purine as well as pyrimidine bases present in this fraction could be responsible for this absorption. The question of whether the ultraviolet spectrum of spinal fluid has diagnostic significance in certain neurologic diseases should be discussed in relation to the chemical compounds responsible for ultraviolet absorption of spinal fluid in health and disease.

Experiments reported here indicate that one of the main components responsible for ultraviolet absorption of spinal fluid is ascorbic acid. The spinal fluid level of this vitamin is very variable among subjects with and without neurologic diseases, and this variation depends to a large extent on factors, such as intake of vitamin C in the diet, which have nothing to do with the presence or absence of a disease of the nervous system. This is confirmed by the fact that, in the series of patients studied here, no correlation existed between the degree of ultraviolet absorption and the presence of neurologic disease. Strait, Aird, and Hrenoff[10] have already stressed the important part played by ascorbic acid in the ultraviolet absorption of spinal fluid. Also, our results do not confirm that the absorption spectra published by Shionoya,[3] Païc,[1] and Scheid[2] are due to cerebral lesions. These authors showed that maximal absorption of spinal fluid occurred between 2,700 and 2,800 Å and admitted that this absorption was due to proteins. These authors could probably not make the very rapid measures of absorption which have become possible with the new type of spectrophotometer now available, and they probably entirely missed the spontaneous decrease of absorption due to ascorbic acid. Their published curves are similar to those we recorded after the disappearance of ascorbic acid.

Our results are in disagreement with the general conclusion of Spiegel-Adolf and associates,[5–9] who have proposed spectrophotometric absorption measurement in the ultraviolet region as a medicolegal criterion of organic lesion in cerebral concussion. These authors, studying the consequence of cerebral concussion in man, obtained a few hours after trauma a specific absorption band at 2,650 Å. Experimental animals showed this same absorption. They thought that this selective absorption was due to the passage into the spinal fluid of products of disintegration of nucleic acids, especially purines and pyrimidines. Also, they showed a parallelism between the evolution of the absorption curves with time in the same patient and the evolution of chromatolysis in the central nervous system described by Windle, Groat, and Fox.[12] These authors found in guinea pigs submitted to acceleration concussion a disruption of the Nissl bodies culminating in chromatolysis. Our analysis of the several factors involved in the selective absorption at 2,650 Å do not add support to this conclusion, which was already made doubtful by the experiments of Strait, Aird, and Hrenoff.[10]

In 1954, Kovacs[4] published a systematic survey of 402 cerebrospinal fluids, including samples from patients with meningitis, poliomyelitis, brain abcess, brain tumor, epilepsy, and psychosis as well as samples from normal individuals suffering from nonneurologic illness. Kovacs described as characteristic of normal spinal fluid curves without definite peak and curves with a peak near 2,800 Å. Spinal fluids from poliomyelitis patients had a selective absorption band at 2,800 Å. These curves are similar to those we obtained after alkalinization or incubation. In some cases—notably of brain tumors—Kovacs obtained curves with multiple absorption bands scattered between 2,400 and 3,000 Å. We have never obtained curves with many peaks, as Kovacs did, and are unable to explain this discrepancy.

CONCLUSION

The data reported here indicate that there was no correlation in a series of 75 patients between the results of spectrophotometric measurement in the ultraviolet range of spinal fluid and the nature of the patients' nervous diseases. In other words, in this series, these spectrophotometric measurements did not contribute to the diagnosis.

The lack of diagnostic significance of changes in the ultraviolet absorption spectrum of spinal fluid is the consequence of the fact that this absorption is conditioned by several factors, some of which have a large range of variation in healthy as well as in sick individuals; among these various factors, the most important appear to be the ascorbic acid content, the protein fraction, and the alkali-stable fraction of the protein-free filtrate of the spinal fluid.

It is possible that a more elaborate study of these factors and others at present unknown may confer diagnostic significance to the spectrophotometric analyses of spinal fluid, but, in its present form, this analysis appears to be essentially noncontributory to the solution of diagnostic problems.

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Arteriovenous vascular malformation of the cervical portion of the vertebral artery

A case report

William H. Faeth, M.D., and Howard W. Dueker, M.D.

INTEREST in cerebrovascular lesions has led to the demonstration of many interesting anomalies. One such curiosity is reported here.

M. S., a 60-year-old white female, was seen in consultation because of a rhythmic hissing sound in the left side of her head. She had noted the rather abrupt onset of this bruit some ten months previously. She had no associated neurologic complaints. Her past history revealed that she had been deaf in the right ear ever since a bout of meningitis in early childhood. Some seventeen months before examination, the patient had fallen and landed on her buttocks, sustaining a compression fracture of the twelfth thoracic vertebra and a mild cerebral concussion but no particular cervical trauma.

Neurologic examination revealed only conduction deafness on the right and a loud systolic bruit over the left mastoid tip which carotid compression could not obliterate.

Roentgenograms of the skull revealed evidence of old mastoiditis.

From the Saint Joseph Hospital, Burbank, Calif.

[A] Anteroposterior and [B] lateral left vertebral angiograms. Note anomalous character of vertebral artery with abnormal communication with deep cervical veins.

Subsequently, the patient was admitted for angiography. A left carotid angiogram was quite normal. The left vertebral angiogram demonstrated a large arteriovenous malformation arising from the cervical portion of the vertebral artery (see figure, A and B). The basilar circulation filled normally above the lesion.

Upon awakening from the angiogram, the patient noted that her bruit had disappeared. She manifested no outward symptoms and was discharged from hospital the next day. A few days later, however, postural vertigo developed, but this gradually cleared over the next few weeks. The neurologic examination remained normal.

DISCUSSION

Whether the trauma which this patient had suffered seven months before the onset of her bruit had produced the arteriovenous fistula or whether it was of spontaneous origin is a matter of speculation. It must be presumed that the angiogram in some way caused a thrombosis of the arteriovenous communication, fortuitously solving the patient's problem.

Effect of antidiuretic hormones on renal sodium and potassium excretion in a patient with traumatic diabetes insipidus

Francis P. Nash, M.D., and Edmund A. Smolik, M.D.

IT IS GENERALLY AGREED that there is a pituitary hormone influence upon the renal excretion of electrolytes. There is, however, disagreement as to whether this influence results in an increased excretion[1] or, as others maintain, a decreased excretion.[2]

We were afforded an opportunity for direct observation of the effect of both pitressin and posterior pituitary hormone on renal sodium and potassium excretion in a patient who had diabetes insipidus after trauma. The data from these studies constitute the basis of this report.

CASE HISTORY

A 19-year-old white man was admitted to the neurosurgical service after an accident in which he was struck by a railroad locomotive. He sustained a compound fracture of the right frontal bone and was unconscious. Twenty-four hours after admission, debridement of the wound was carried out.

His postoperative course was one of steady resolution of the neurologic deficits. The wound healed per primam. One month after admission, he was completely alert and oriented in all spheres. He had full motor power. He did have residual loss of upward gaze, bitemporal hemianopsia, and severe polyuria and polydipsia.

Laboratory data. The urinary output was 9,000 to 10,000 cc. per twenty-four hours. The urinary specific gravity ranged from 1.001 to 1.004. These other parameters were within the range of laboratory normal: hemogram, glucose tolerance tests, basal metabolic rate, protein-bound iodine, blood urea nitrogen, and urea clearance. The serum electrolyte values remained within normal levels with adequate oral electrolyte intake. It was noted, however, that the administration of antidiuretic substances not only resulted in a decrease in urine volume and an increase in urine specific gravity but also resulted in a transient increase in Na^+ and K^+ urinary excretion. It appeared that there was a quantitative difference in the excretion of these electrolytes after the administration of pitressin or posterior pituitary hormone. For this reason, more detailed control studies were undertaken.

METHODS

During these determinations, the patient was maintained on complete bed rest in order to avoid any postural influence on renal excretion. He was provided with adequate fluids to maintain a normal degree of hydration. The total sodium and potassium intake was determined and maintained at constant levels during the period of study. The control excretion rates of sodium and potassium were determined on urinary specimens collected at thirty-minute intervals via an indwelling urethral catheter.

Under this condition of fixed sodium and potassium availability, posterior pituitary hormone, U.S.P. (the water-soluble principle of the posterior lobe of cattle pituitary body), was given intramuscularly in a 1-cc. dose. After the administration of this substance, the urinary specimens were again collected at thirty-minute intervals and the sodium and potassium content of each was determined.

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The serum sodium and potassium concentrations were determined at two-hour intervals.

The next day, under like balanced conditions, pitressin, NNR (beta-hypophamine), was given intramuscularly in a 1-cc. dose. Again, the urinary specimens were collected at thirty-minute intervals and the sodium and potassium content of each was determined. As before, serum sodium and potassium concentrations were determined at two-hour intervals.

These serial determinations of both urinary and plasma sodium and potassium concentrations were made utilizing the Coleman (Model 21) flame photometer. The specific procedures followed are specified in Bulletin D-248 (operating instructions) for this flame photometer.

RESULTS

The administration of posterior pituitary hormone or of pitressin reduced the rate of urinary excretion to 2,500 or 3,500 cc. per twenty-four hours from 9,000 to 10,000 cc. The maximal urinary specific gravity rise after the administration of either substance was between 1.007 and 1.010. In general, the antidiuretic effect of the posterior pituitary hormone was a bit more marked per unit given than was the effect of pitressin.

One hour after administration of the posterior pituitary hormone, an increase in the concentration of sodium and potassium per cubic centimeter of urine was noted. The rate of increased concentration was greater for sodium than potassium. This reached a maximum two and one-half hours after administration of the posterior pituitary hormone and remained above the control concentration levels for four and one-half hours.

The maximal increase in the concentration of potassium per cubic centimeter of urine was reached three hours after the administration of the posterior pituitary hormone and remained above the control concentrations for seven hours (Fig. 1).

One hour after administration of pitressin, there was an increase in both the sodium and potassium concentration per cubic centimeter of urine. However, the increased concentration was greater for potassium than sodium, the reverse of that noted after administration of posterior pituitary hormone.

The concentration of potassium per cubic centimeter of urine reached its maximum two hours after administration of pitressin. This increase persisted for only three and one-half hours. The increased concentration of sodium per cubic centimeter of urine reached its maximum three and one-half hours after the administration of pitressin. This rate of increase persisted for four hours (Fig. 2). The serum electrolytes remained within the range of normal values throughout the control and post-injection periods.

DISCUSSION

Some investigators have concluded that there is an increased renal sodium excretion

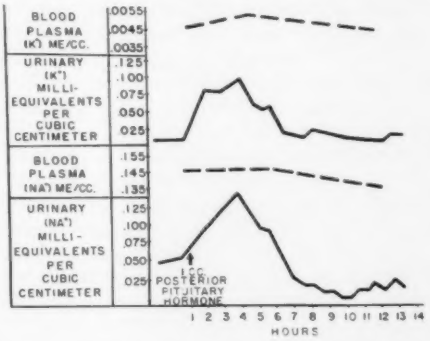

Fig. 1. Changes in urinary concentration of sodium and potassium after administration of posterior pituitary hormone

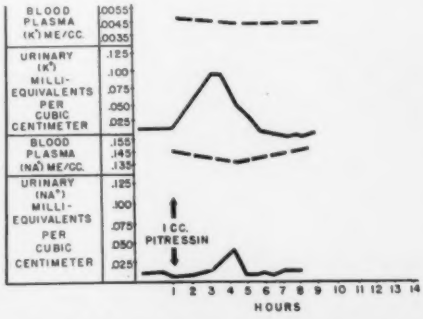

Fig. 2. Changes in urinary concentration of sodium and potassium after administration of pitressin

after the administration of posterior pituitary hormone.[3] Other reports have described a decrease in the renal sodium excretion after the giving of posterior pituitary hormone.[2] Heller and Stephenson[4] concluded that the rate of potassium excretion was increased and the rate of sodium excretion decreased after the administration of pitressin. Thorn and Stein[5] found that the administration of pitressin decreased urinary sodium excretion in a patient with diabetes insipidus.

Blomhert[6] concluded from his work that alterations in electrolyte excretion that accompany the administration of antidiuretic substances were not the direct result of the action of these substances on the kidney but were related to changes in hydration of the patient. He described an increase in the sodium excretion and a decrease in the potassium urinary excretion in patients with diabetes insipidus given antidiuretic hormones.

The patient reported here, while in a state of adequate hydration, did have a transient increase in urinary excretion and concentration of both sodium and potassium after the administration of either posterior pituitary hormone or pitressin. The sodiouritic action was quantitatively greater after administration of posterior pituitary hormone than pitressin. The reverse was true in regard to potassium excretion.

CONCLUSIONS

1. The administration of both posterior pituitary hormone (U.S.P.) and pitressin (NNR) in a normally hydrated patient with traumatic diabetes insipidus was followed by a transient increase in the rate of urinary excretion and concentration of both sodium and potassium.

2. The increase in sodium concentration per cubic centimeter of urine was greater but less prolonged than that of potassium after administration of posterior pituitary hormone.

3. The increase in potassium concentration per cubic centimeter of urine was greater and more prolonged than that of sodium after administration of pitressin.

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Hemangiopericytoma of the brain

Joseph V. McDonald, M.D., and Roger Terry, M.D.

In 1942, Stout and Murray[1] first described the hemangiopericytoma as a separate entity among the vascular tumors. They felt that the tumor took origin from the pericytes of Zimmermann, branching contractile cells which lie along the external walls of the capillaries. Logically, because of the almost universal distribution of capillaries, the neoplasm would be expected to occur in many sites throughout the body. This was proved to be so, for, while the hemangiopericytoma has occurred most commonly in the skin and subcutaneous tissues, it has also been reported as arising within the orbit, uterus, retroperitoneal tissues and omentum, gut, and bone. A few instances of primary or secondary involvement of the meninges external to the brain have also been reported, but no such neoplasm has been described as originating within the ventricular system or within the brain itself.

This paper describes an hemangiopericytoma which arose from the choroid plexus of the right lateral ventricle and reviews the literature concerning involvement of the central nervous system by this tumor.

CASE REPORT

H. W. (S. M. H. No. 440200), a 55-year-old shoe salesman, was admitted to the Strong Memorial Hospital on October 15, 1957. His chief complaint was "petit mal for several months."

He had been well until May 1957, when he began having episodes of loss of equilibrium in which he always fell to the left. These occurred suddenly and were so violent that he usually fell to the floor, remaining there for two or three minutes. The attacks occurred almost every morning. They were not accompanied by vertigo, nausea, vomiting, clonus, or subsequent weakness of the extremities.

Early in September 1957, he had a similar episode but this time became unconscious and fell down a flight of stairs, fracturing some ribs. He was unconscious for five minutes. Thereafter, he felt that his equilibrium was poor at all times, and he could walk only with difficulty. Two weeks before his admission, he dropped a cigarette from his left hand. He was unable to tell that anything had been in the hand. He leaned over to pick up the cigarette and fell forward because of poor equilibrium. When someone handed him the cigarette, he tried to say thanks but spoke a jargon.

One week before admission, while writing his name at work, he thought that he was forming the words properly but was told by an associate that he was writing a scrawl. He attempted to tell his friend to leave him alone, but, again, he later learned that all he had done was speak in a jargon.

His wife had noted that, for the two or three months before his admission, he had been inappropriately facetious and had suffered a change in personality. However, he had never been disoriented and had had no difficulties in calculation or in making change at work.

At neurologic examination, he was jovial. He was emotionally concerned about his ailment and exhibited emotional lability. He was well oriented and could do simple sums and serial 7's without difficulty. There were no abnormalities of the skull. Visual field examination showed a left superior temporal quadrantic field defect. He had no papilledema nor any other abnormality in the cranial nerve examination. The tendon reflexes were bilaterally equal and normal. There were no Hoffmann or Babinski signs. The abdominal and cremasteric reflexes were normal. He had no demonstrable sensory loss, astereognosis, or loss of figure-writing sense in

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either palm. When he stood, he consistently fell to the left.

A lumbar puncture was performed, and the initial pressure in the lateral recumbent position was 330 mm. The spinal fluid protein was 225 mg. per cent. The remainder of the spinal fluid findings were normal.

Skull roentgenograms were normal; the pineal gland was not calcified. An electroencephalogram showed a focus of slow wave activity in the right temporal region. A carotid angiogram showed a shift of the anterior cerebral arteries to the left. Some of the branches of the right middle cerebral artery appeared elevated, and there was a tumor stain, oval in shape and about 3 cm. in diameter, deep in the right parietal lobe extending just beyond the midline (Fig. 1A and B).

Ventriculography was performed. The right lateral ventricle could not be tapped, and no air passed into it after 25 cc. of air had been placed into the left lateral ventricle. Films showed a dilated left lateral ventricle with a marked shift of the third ventricle to the left side (Fig. 2).

A right temporoparietal craniotomy was then done. The brain was entered in the posterior temporal region. At a depth of 3 cm., a firm, round, purple tumor was found lying within the right lateral ventricle which was collapsed. The tumor was about 3.5 cm. in diameter. The choroid plexus lay medial to and inferior to the tumor, which was attached to it in the region of the trigone. The tumor did not seem to invade the white matter or the ependyma. The choroid plexus and the mass were removed. The point of the tumor's attachment was heavily coagulated, and 3 silver clips were placed there. The operator was surprised to find that, instead of being dilated, the right lateral ventricle was collapsed and contained practically no fluid.

During the first postoperative week, the patient had a loss of cortical sensation in the left hand as well as a paresis of his left leg. However, by the time of his discharge two and one-half weeks after surgery, these signs had disappeared. He no longer had any difficulty with his equilibrium and could walk well. He had no difficulty in writing or speaking. An examination of the visual fields at that time

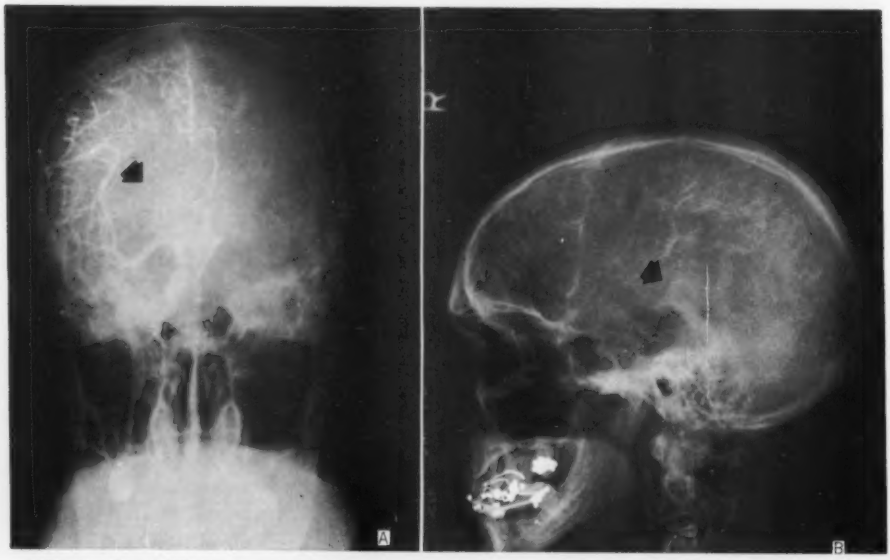

Fig. 1. [A and B] Arteriograms showing a roun d tumor stain deep in right parietal region

showed left homonymous hemianopsia involving all of the superior quadrant and about one-half of the inferior quadrant.

A course of radiation therapy was administered following surgery. A total tumor dose of 5,025 r was given within thirty-seven days.

He was examined last in December 1960, at which time his condition was unchanged, and there was no evidence of recurrence of the tumor.

The pathologic report described the tumor as a solitary reddish nodule with a smooth surface. It was fairly well circumscribed and could be separated readily from the surrounding yellowish-white brain tissue. When sectioned, the tumor had a soft grayish-yellow center, with a dark red hemorrhagic periphery.

The histologic report was as follows: Microscopically, the nodule is made up of large and small vascular spaces lined by a single endothelial layer. Around these are densely packed masses of cells having a finely granular eosinophilic to clear cytoplasm with an indistinct cell border. Their nuclei vary in size and shape from fusiform to round and have a reticulated light-staining nucleoplasm. Mitotic figures are rare. Between many of the these cells, delicate strands of collagen are seen (Fig. 3).

Laidlaw reticulin silver stains demonstrate that the tumor cells lie outside the reticulin sheaths of the capillaries and confirm the fact that fine reticulin fibers separate and surround most of the tumor cells (Fig. 4).

The border between the tumor mass and the cerebrum is distinct, and, although no capsule is present, there is a zone of hemorrhage between the two. On the cerebral side, there is compression of the brain substance, with focal hemorrhage and perivascular round cell infiltration. There is no invasion of the brain by the tumor. Other slides show the tumor immediately adjacent to the choroid plexus (Figs. 5 and 6).

Microscopic slides were sent to Dr. Arthur P. Stout who concurred in the diagnosis of hemangiopericytoma.[2]

Fig. 2. Ventriculogram showing lack of filling of right lateral ventricle and shift to left

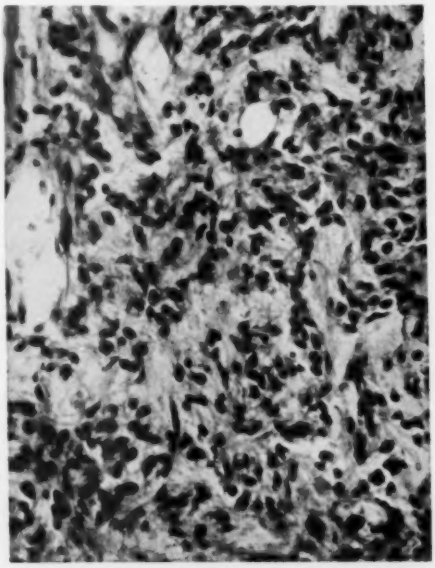

Fig. 3. Photomicrograph showing vascular spaces and extraluminal position of tumor cells. Hematoxylin and eosin. × 300

DISCUSSION

Typically, the hemangiopericytoma is a circumscribed, nodular, pink-gray or purple mass which may be partially calcified. In about a third of the cases, it is locally invasive or there

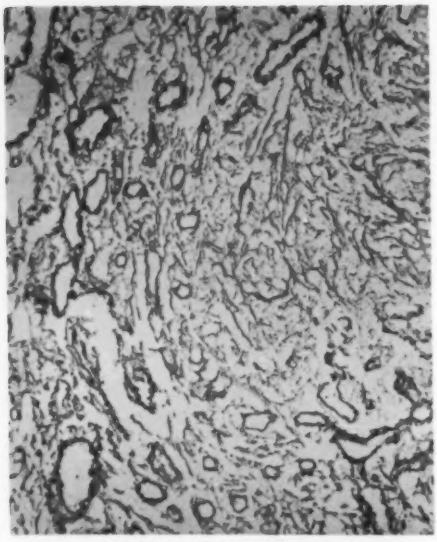

Fig. 4. Laidlaw silver stain demonstrating numerous capillaries and strands of reticulin extending around extraluminal tumor cells. × 120

are distant metastases. Microscopically, it is not well encapsulated. As Stout[3] has pointed out, there is a lavish proliferation of capillaries which may be collapsed or patent but which have an essentially normal endothelium. These vessels have a well-defined connective tissue sheath which is clearly revealed by silver stains. It is characteristic of the tumor that outside the sheath and not within the vessels lie the densely packed, round to spindle-shaped tumor cells which are believed to be derived from the pericytes. Strands of reticulin extend in all directions separating and surrounding these cells, which are densely packed and have no precise architectural pattern. This is in contrast to the glomus tumor which is well encapsulated, contains many nerve fibers, and has a sharply defined organoid appearance and to the hemangioendothelioma in which the tumor cells are intraluminal.

In 1949, Stout[2] added 25 new cases of hemangiopericytoma to the 10 previously described. In Case 24 in the second series, the cerebral meninges were involved. The tumor occurred in a 27-year-old woman who was a

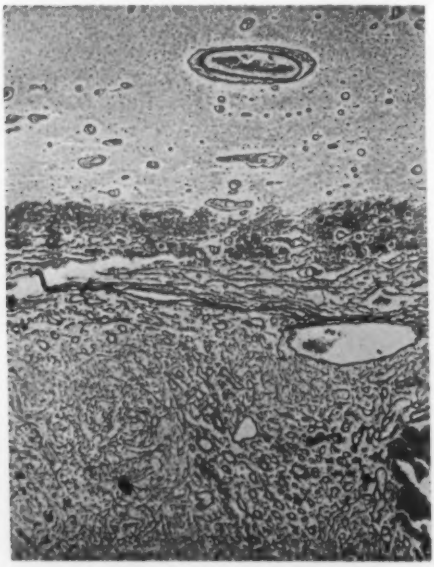

Fig. 5. Illustration showing clear-cut but hemorrhagic border of tumor. × 48

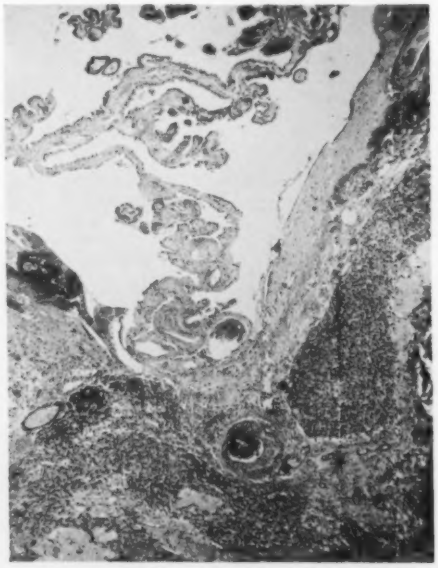

Fig. 6. Photomicrograph showing attachment of tumor to choroid plexus. × 30

patient of Dr. Sam Snodgrass of Galveston. She had struck her head in an automobile accident, and a lump appeared in her scalp but did not enlarge until ten months had passed. For two months, the mass continued to increase in size. Surgery was then performed. A 3-cm. skull defect was found through which the subcutaneous tumor communicated with a larger intracranial one. Because of severe hemorrhage, the patient died. At autopsy, a 4-cm. tumor was found on the dura. It had occluded the superior longitudinal sinus and extended between the hemispheres. It compressed the right hemisphere but did not invade it. Precisely where this tumor originated is uncertain because of the involvement of scalp, skull, and dura, but there can be no doubt about the case described by Begg and Garret.[4] Their patient was a 63-year-old woman with progressive right hemiplegia. Craniotomy was performed, and a left parietocentral tumor was removed. It was adherent to the dura and compressed but did not invade the brain. The patient recovered from her paresis and eight years later was perfectly well.[5]

Begg[4] also pointed out that among the tumors described by Cushing and Eisenhardt[6] in their classic monograph on meningiomas was one group—Type IV, Variant I—which appeared to fit the description of the hemangiopericytoma.

This is of interest if one analyzes the natural history of the 6 lesions included in that group because several unusual features become apparent. All of these tumors were extracerebral; 1 lay in the temporal fossa while the remaining 5 were peritorcular in distribution. The patients were 44, 34, 31, 30, 28, and 21 years old, a relatively young group to have meningiomas. These 6 patients underwent 22 operations because of repeated rapid recurrences of their tumors. In none of them was the tumor removed completely, and they all died. Only 1 survived for five years, and he succumbed after a second craniotomy for the same tumor.

This is in contrast to the other 7 patients in Cushing's series who had peritorcular meningiomas of some other variety; 3 of these patients died. Postoperative actinomycotic infection occurred in 1, while the second was found to have a glioma of the corpus callosum as well as a meningioma. The third lived for five years and five months and then died of a recurrence. His tumor was of Type IV, Variant II, a type differing only slightly histologically from the hemangiopericytoma but evidently very definitely containing some meningiothelial cells. These statistics show that the hemangiopericytoma is a much more lethal tumor than the meningioma.

Fisher, Davis, and Lemmen[7] added another highly malignant tumor to the list of these lesions when they described a 24-year-old man who was found to have an hemangiopericytoma in the left temporal fossa. Arteriography revealed a tumor stain. He underwent several craniotomies, but the extremely vascular and invasive tumor always recurred very rapidly, and he died within two years.

Peace[8] added an interesting case which occurred in an infant who died shortly after birth. The child was well until the third day of life, when he became listless and left hemiplegia and fixed, dilated right pupil developed. Subdural punctures were normal, but bloody spinal fluid was obtained by lumbar puncture. On the next day the child died. At autopsy, a stellate fracture of the right parietal bone was found and was attributed to obstetric trauma. On the right side, the dura was tense and beneath it lay a hematoma and a spongy purple tumor which was 6 cm. in diameter. It had replaced much of the right hemisphere. There was no connection between the tumor and the border of the right lateral ventricle, and the mass was "well demarcated" from the adjacent brain tissue, which was not abnormal save for compression. Histologically, there was no evidence of invasion of or attachment to the brain.

That these tumors may also involve the spinal canal was demonstrated by the case reported by Schirger and his associates[9] at the Mayo Clinic. In 1931, a laminectomy was performed in a 33-year-old woman because of leg numbness and pain in the left shoulder. A pink tumor, which appeared to arise from the left second intercostal nerve, was removed from the extradural space, but some tumor tissue was seen to pass anteriorly into the bone. It was diagnosed then as a cellular hemangioendothelioma, and x-ray treatment

was given postoperatively. She made an excellent recovery.

Twenty-six years later, in 1957, she returned because of a recurrence of symptoms. Roentgenograms showed a mass in the apex of the left chest. The medial end of the left third rib and the pedicle of the third thoracic vertebra on that side were destroyed. A myelogram revealed almost a complete blockage of the spinal canal at the fourth thoracic level by an extradural mass. A second laminectomy was done, but the tumor could be removed only partially. X-ray treatment was given again. At this time, the old slides were reviewed and the tumor was found to be identical with the new specimen. The diagnosis of malignant hemangiopericytoma was made.

As far as we have been able to ascertain, there are then 12 reported cases of involvement of the brain or spinal cord by hemangiopericytoma in the literature; 1 of these was an intraspinal extradural mass in the upper thoracic region. Another, the subject of this report, arose within the brain from the choroid plexus of the lateral ventricle. The remaining 10 cases were all intradural extracerebral tumors which compressed the hemispheres; 1 patient was a newborn infant, while 4 were in the third decade of life and another 4 in the fourth decade. The remaining 3 tumors occurred in patients who were 44, 55, and 63 years of age, indicating that the peak incidence of this tumor in the central nervous system is during early adult life.

It is generally stated that about one-third of the hemangiopericytomas elsewhere in the body are malignant and that the remainder can be readily excised with an excellent life expectancy. Among the reported 11 patients who have undergone surgery because of involvement of the central nervous system, the outcome has been much worse. A woman has had 2 laminectomies, twenty-six years apart, but it is known that part of the tumor was left behind at the second operation. Of the remaining 10 patients, 8 have died because of recurrences or inoperability.* The 2 who survived appear to have been cured, but even here the prognosis must be guarded because of the twenty-six year interval before recurrence in the case reported from the Mayo Clinic and the five-year interval in 1 of Dr. Cushing's cases.

CONCLUSION

A case in which an hemangiopericytoma arising from the choroid plexus was removed from the lateral ventricle of a 55-year-old man has been reported. More than three years later, he was well with no evidence of recurrence.

A review of the literature in which this tumor was described as having involved the brain and spinal cord has been made. While the gross appearance of the hemangiopericytoma is similar to that of a meningioma and while the former has occurred in many of the same sites, this review indicates that it is a much more malignant meningeal tumor. Therefore, an accurate histologic diagnosis of hemangiopericytoma is important clinically for, when it is made, a knowledge of the natural history of the tumor might justify bold attempts at wide resection to prevent a recurrence.

*Dr. Begg has written us recently about another patient who has survived for one year after the removal of an hemangiopericytoma which arose in the meninges overlying the cerebrum.

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Evaluation of controlled digital carotid artery compression in cerebrovascular insufficiency

Carotid sinus (cardioinhibitory type) response

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IT HAS BEEN KNOWN for many years that there is an increased incidence of hypersensitive carotid sinus in older persons[1] and in patients with "arteriosclerosis"[2] or "cerebral disease."[3] Hering, to whom most of the credit for elucidating the carotid sinus reflex is given, had his interest aroused in this reflex by pressing on the neck of an "old lady" while studying Tschermak's Vagusdruckversuch and finding that it produced marked cardiac slowing.[4] However, the earliest reference I can find that noted a relation between a hypersensitive carotid sinus and a proved spontaneous thrombosis of the internal carotid artery was that of Chao and associates[5] in 1938. Then, Galdston and associates[6] in 1941 reported 2 other cases of spontaneous carotid artery thrombosis associated with increased carotid sinus sensitivity. In 1942, Engel and Margolin[7] stated that "A hypersensitive carotid sinus is generally secondary to disease directly or indirectly involving some portion of the reflex arc. Thus, it is frequently associated with generalized cerebral and coronary arteriosclerosis and with local disease of the carotid arteries." In the more recent literature, however, this relationship has been commented on only rarely; it is unusual to see statements such as Ottenberg's[8] that ". . . the clinical picture [of occlusion of the internal carotid artery] is characterized by a clear-cut and specific triad: (a) carotid sinus sensitivity . . ." or Meyer, Leiderman, and Denny-Brown's[9] that there is ". . . frequent association of hypersensitivity of the carotid sinus with disease of the carotid arteries." The exceptions to this lack of interest in this association are the reports of cases of "pulseless disease."[10–13]

In a project to evaluate digital compression of the carotid artery in the diagnosis of cerebrovascular insufficiency, the results of cerebral ischemia due to the occlusion of the artery by manual compression have been previously described.[14] The cardioinhibitory effect of a sensitive carotid sinus may be the other manifestation of compression of the carotid artery; this present paper deals with this particular phenomenon.

TECHNIC

The carotid artery was digitally compressed unilaterally on each side twice. The compression was continued for up to about thirty seconds each time unless there was a significant cardiac slowing or change in the electroencephalogram. The patient was either lying supine or sitting in a semireclining position. Sudden—in contrast to gradual—compression was applied over the carotid artery at about the angle of the jaw; it was strong enough to occlude the pulse distally. Before, during, and after the compression, an electroencephalogram and electrocardiogram were obtained simultaneously. The electrocardiogram was a nonstandard lead obtained between the precordium and a scalp electrode.

Most patients were chosen only on the basis

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of consecutive referrals to the electroencephalography laboratory; however, patients with increased intracranial pressure, recent cerebral or subarachnoid hemorrhage, or recent myocardial infarctions were routinely excluded. After this entire project was completed, each case was reviewed; the decision was then made (independent of the effect of carotid compression, of course) as to whether the patient did or did not have cerebrovascular insufficiency (CVI) and, if he did, whether it was unilateral or bilateral carotid and/or basilar "tree" insufficiency. Insufficiency was defined as enough impairment of arterial blood supply to the brain to cause a clinically discernible amount of brain malfunction; the degree of vascular insufficiency varied up to total occlusion of a major vessel. Since, at times, it was difficult enough to diagnose which of these major "trees" were at fault, it was decided to limit the divisions of arterial insufficiency to carotid and basilar "trees" rather than to attempt any-

TABLE 1
RESULTS OF DIGITAL CAROTID COMPRESSION

	Age groups							
	20	*30*	*40*	*50*	*60*	*70*	*80*	*Total*
No CVI								
Total patients	19	53	62	51	83	10	2	280
VR* with IR†	0	0	0	2	9	2	0	13
VR without IR	0	0	4	3	15	1	1	24
IR without VR	0	2	4	4	7	1	0	18
Unilateral carotid CVI								
Total patients	0	6	4	17	32	9	2	70
VR with IR	0	0	0	9	4	1	0	14
VR without IR	0	0	0	3	4	1	0	8
IR without VR	0	2	2	0	4	1	0	9
Bilateral carotid CVI								
Total patients	0	1	4	4	33	5	2	49
VR with IR	0	1	2	0	6	2	0	11
VR without IR	0	0	1	0	7	2	1	11
IR without VR	0	0	0	1	4	0	1	6
Basilar only CVI								
Total patients	1	0	1	5	16	3	0	26
VR with IR	0	0	0	0	4	1	0	5
VR without IR	0	0	0	1	1	1	0	3
IR without VR	0	0	1	1	5	0	0	7
Basilar plus unilateral carotid CVI								
Total patients	0	1	0	1	4	0	0	6
VR with IR	0	0	0	0	0	0	0	0
VR without IR	0	0	0	0	2	0	0	2
IR without VR	0	0	0	0	0	0	0	0
Basilar plus bilateral carotid CVI								
Total patients	0	0	1	3	9	2	0	15
VR with IR	0	0	1	1	1	0	0	3
VR without IR	0	0	0	0	2	0	0	2
IR without VR	0	0	0	0	2	1	0	3

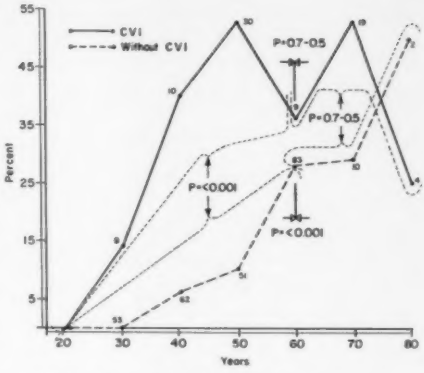
* Vagal response
† Ischemic response

thing more specific. The vast majority of patients were examined by the Neurological and/or Neurosurgical Sections; the few remaining were seen only by the Internal Medicine Service. The diagnosis of CVI was based wholly on clinical signs and symptoms. The shortcomings of this technic were appreciated, but, since CVI is a pathophysiologic entity, anything short of accurate measurements of cerebral blood flow (and this is to be questioned, too) would be open to even greater inaccuracies. Those patients who had angiographic evidence of total or near total occlusion—that is, "good" anatomic evidence that there must have been insufficiency—invariably had signs and symptoms sufficient to make a diagnosis of CVI on clinical grounds. On the other hand, several patients who showed angiographically mild or slight evidence of cerebrovascular disease gave no evidence clinically of the syndrome of CVI.

An abnormal carotid sinus effect due to carotid compression was defined as a decrease of the pulse rate to at least one-half of the precompression rate; this "cardioinhibitory" type of carotid sinus effect is ultimately mediated over the vagus, that is, a vagal response. This criterion of abnormality was used rather than a complete cardiac standstill, since it was difficult at times to know whether there was indeed a standstill before the compression was relieved or whether the heart would have continued beating, though at a very slow rate, if the compression had been continued. Because of the potential danger of a too prolonged cardiac standstill, no attempt was made to challenge the patient and, once a "sufficient" degree of slowing was noted, the pressure was released.

If the patient demonstrated a vagal response, he was given enough atropine, usually 1.2 mg., subcutaneously to block this and the test was repeated in order to evaluate the effects of carotid occlusion—using the electroencephalogram as an end point—independent of the carotid sinus effect. The relation of the ischemic response (that is, electroencephalographic slowing secondary to carotid artery occlusion) has been discussed elsewhere.[14]

The decision of whether any given patient had a vagal response or an ischemic response was based upon all his compression tests and not just one, since results were by no means the same each time a carotid was compressed.



Comparison of the frequency of occurrence of vagal response in patients with and without CVI according to age. The small numbers accompanying each point indicate the number of patients in each age group; note that, at extremities of the graph, some groups are too small to be considered significant.

RESULTS

Carotid sinuses were tested in 479 patients on one or more occasions. Of these, 446 patients met the following criteria: [1] there was definite clinical basis for a diagnosis of either no CVI, or, if the patient did have CVI, the particular vascular "tree" or "trees" which were insufficient could be identified; [2] the electroencephalographic records that were obtained were free enough of artifact to be interpreted reliably. It is with this group of 446 that the following report deals. The results are tabulated in Table 1.

There were 280 patients without CVI, and 166 patients had localizable CVI.

Is a vagal response useful in differentiating patients with CVI from those without CVI? When frequencies of the occurrence of vagal response in patients with CVI and in patients without CVI are compared according to age (see graph), the distribution suggests [1] that the frequency of vagal response remains about the same regardless of age in patients with CVI (the probability that the difference between those 60* and older is due to chance

*Median group of our age distribution was 60.

alone is high—p = 0.7–0.5) and [2] that there is an increasing frequency of vagal response with increasing age in patients without CVI (this can be seen from the slope of the curve; also, the probability that the difference in frequency of vagal response between patients without CVI under 60 as compared to those 60 or older being due to chance alone is very poor—p = <0.001). It will also be seen from the graph that, in patients under 60, the probability that the difference in frequency of vagal response in those with CVI and in those without CVI being due to chance alone is very poor (p = <0.001), whereas a similar comparison in patients 60 or older shows that the difference in frequency of vagal response between those with CVI and those without CVI is probably due to chance alone (p = 0.5–0.7). Hence, a vagal response in a patient under 60 may be of value in the diagnosis of CVI, but in patients 60 or over such a finding does not materially aid in making a diagnosis.

Is a vagal response more likely to occur in patients 60 or older with one particular type of cerebrovascular "tree" insufficiency than any other? When the frequency of vagal response in patients with a particular type of CVI—unilateral carotid (without basilar), bilateral carotid (without basilar), basilar (without carotid), or basilar with either unilateral or bilateral carotid "tree" insufficiency—was compared with the frequency of vagal response in patients without CVI, the only comparison that seemed to offer even a suggestion that the differences in vagal response frequency might be due to factors other than chance was the comparison between patients with bilateral carotid "tree" insufficiency and those without CVI (p = .1–.2) (Table 2).

TABLE 2
FREQUENCY OF VAGAL RESPONSE

	Vagal response	*Total patients*	*Vagal response*	x^2	*p*
No CVI	28	95	29		
Unilateral carotid CVI	10	43	23	0.77	.7
Bilateral carotid CVI	18	40	45	2.48	.1–.2
Basilar CVI	7	19	37	0.30	.5–.7

Does the side from which the vagal response can be elicited aid in lateralizing the carotid "tree" insufficiency? In 41 patients who had at least a unilateral carotid angiogram, a total occlusion of the carotid was demonstrated 5 times (Table 3A); a vagal response was obtained in 4 of these patients, each time by compression of the side opposite to the occlusion. In 1 patient with clinical evidence of bilateral carotid "tree" insufficiency and angiographic evidence of partial occlusion of the right internal carotid, a vagal response was obtained by compression of either carotid. Based on clinical impressions, a unilateral vagal response was obtained in 5 patients when the same side as the unilateral carotid "tree" CVI was compressed while, in another 18 patients, it was obtained by compression of the "good" carotid (Table 3B). A unilateral vagal response was obtained by compression of the carotid on the same side as the electroencephalographic focus in 6 patients who had unilateral carotid "tree" CVI only with focally abnormal electroencephalograms, but, in 11 patients, the side from which the vagal response could be obtained was the side opposite to the electroencephalographic focus (Table 3C). Hence, a unilateral vagal response is probably obtained from compression of the "good" side in a total carotid artery occlusion and, though usually it can be elicited from compression of the "good" side in a partial occlusion, it may on occasion be obtained from the diseased side.

If a patient has both a vagal and an ischemic response, is this any better basis for entertaining the diagnosis of CVI than if he has only one of these responses? In patients under 60, the presence of both a vagal and an ischemic response rather than just one or the other further increases the likelihood of the patient having CVI. This is borne out by the figures in Table 4A. The number of patients is too small to allow for any statistical manipulation other than the calculation of percentages. However, it will be noted that both a vagal and an ischemic response occurred in only 0.9% of patients without CVI (compared to a vagal response only in 3.3% and ischemic response only in 12.2%), while both a vagal

TABLE 3
RELATIONSHIP OF POSITIONS OF CVI AND VAGAL RESPONSE

A.

Angiogram done on	*Occlusion of*	*Clinically CVI on*	*Vagal response*
Left, right	Right internal carotid	Left and right carotid	Left
Left, right	Left internal carotid	Left and right carotid	Right
Left, right	Left internal carotid	Left carotid	Right
Left	Left internal carotid	Left and right carotid	Right
Left	Left internal carotid	Left carotid	None
Left	Left internal carotid (incomplete)	Left carotid	None
Right	Right internal carotid (incomplete)	Left and right carotid	Right

B.

	Vagal response
Clinically CVI on same side	5
Clinically CVI on opposite side	8

C.

	Vagal response
EEG focus on same side	6
EEG focus on opposite side	11

and an ischemic response occurred in 28.6% of patients with CVI (compared to a vagal response only in 12.2% and an ischemic response only in 12.2%). In patients 60 or over (Table 4B), there is a good probability that chance alone can explain the difference in frequency of the occurrence of a vagal plus an ischemic response between the group with CVI and the group without CVI ($p = .3–.5$); therefore, this particular combination of findings is of no value in attempting to diagnose CVI in patients 60 or older.

A sensitive carotid sinus has been reported to be a common finding in patients with coronary artery disease. Since this is usually due to atherosclerosis, as is carotid artery disease, could the vagal response that was obtained be a reflection of an associated disease rather than be primarily related to the carotid artery disease? In an attempt to answer this, the problem was approached in 2 ways. First, and in a more general way, all patients with any evidence of vascular disease (hypertension,

TABLE 4
INFLUENCE OF VAGAL AND ISCHEMIC RESPONSES ON PRESENCE OF CVI

A.

	Ischemic plus vagal response		*Vagal response only*		*Vagal response only*	
Age	*Without CVI*	*With CVI*	*Without CVI*	*With CVI*	*Without CVI*	*With CVI*
20	0	0	0	0	0	0
30	0	1	0	1	2	1
40	0	3	4	1	4	3
50	2	10	3	4	4	2
Total	2	14	7	6	10	6
% of total patients	0.9	28.6	3.3	12.2	4.7	12.2

B.

	Ischemic plus vagal response	*Total number of patients*		*Per cent*
Without CVI	11	95	$x^2 = .64$	12
With CVI	19	117	$p = .3–.5$	6

retinal arteriosclerosis, coronary artery disease, or absent peripheral pulses) throughout the body (labeled "systemic disease") were grouped together. The frequency of vagal response was then compared between groups having various combinations of CVI and systemic disease. The results are listed in (Table 5A): [1] there was no significant difference in the frequency of vagal response between patients with both CVI and systemic disease and patients with CVI but without systemic disease ($p = 0.8–0.7$); [2] patients without CVI but with systemic disease had a significantly greater frequency of vagal response than those without either CVI or systemic disease ($p = <.001$); and [3] of particular interest, patients with CVI but without systemic disease had a significantly greater frequency of vagal response than those without CVI but with systemic disease ($p = <0.05$). Therefore, it seems quite reasonable to believe that cerebrovascular disease per se is a more important factor than systemic disease as defined here in the increased sensitivity of the carotid sinus in many of our cases.

In regard to the more specific point of coronary artery disease (as manifest by definite angina, electrocardiographic findings, or frank history of myocardial infarction—(Table 5B), the number of cases in our series is relatively small. However, the frequency of vagal response in patients with carotid "tree" CVI (without basilar CVI) and without coronary artery disease is about the same in this series as in patients with coronary artery disease and without CVI, and both these groups are more likely to have a vagal response than patients with basilar "tree" (without carotid CVI) insufficiency and without coronary artery disease. Hence, a patient with CVI may well have a vagal response independent of any coronary artery insufficiency (as defined here) and vice versa, but the obtaining of a vagal response in a patient with one of these arterial diseases and suspected of having the other must be interpreted with considerable caution.

Since patients with CVI have an increased incidence of carotid sinus sensitivity, can this hypersensitivity be an important factor in producing transient minor episodes of CVI? That a hypersensitive carotid sinus might precipitate a fall in blood pressure and, hence, an episode of CVI has been suggested by several authors.[9,15] It might also be suggested that, if this is one of the mechanisms in producing transient falls in blood pressure (either by a direct effect on the peripheral arteries, that is, a "depressor" type of carotid sinus effect, or, more likely, by producing an asystole), efforts

TABLE 5

FREQUENCY OF VAGAL RESPONSE WITH SYSTEMIC AND CORONARY DISEASE

A.

Vagal response is more common here than	*here*	*p*
with CVI with systemic disease	with CVI without systemic disease	0.8–0.7
without CVI with systemic disease	without CVI without systemic disease	.001
with CVI without systemic disease	without CVI without systemic disease	<.001
with CVI without systemic disease	without CVI with systemic disease	<.05

B.

	Total number of patients	*Number with vagal response*	*Per cent with vagal response*	*Ages* 40	50	60	70
Carotid CVI without coronary disease	32	13	41	1	5	6	1
Basilar CVI without coronary disease	9	1	11			1	
Coronary disease without CVI	13	5	38			4	1

should be made to block the carotid sinus with atropinization, surgery, or roentgen therapy.[16,17] It may also follow that some of the favorable results from surgical manipulation about the carotid artery might be due to the mechanical stripping of the vessel and hence damage to the nerve from the carotid sinus.

Some degree of substantiation for the idea that the carotid sinus plays a significant role in transient attacks of CVI might be obtained if patients with a history of transient minor episodes of CVI were shown to be more likely to have a vagal response than patients who had a single, nontransient episode of CVI. Therefore, patients with unilateral carotid CVI were divided into 2 groups: [1] those who had experienced transient episodes of CVI and [2] those who had had only a single major episode. The frequency of vagal response in each group was then compared (Table 6). It is evident that the number of patients who had a vagal response in each group is too small to allow for any dogmatic conclusion, but there does not appear to be any very striking difference in the incidence of carotid sinus hypersensitivity in patients with transient episodes of CVI and those with but a single major attack.

In regard to this problem, it is well to recall the difference between carotid sinus syndrome and a hypersensitive carotid sinus.[18] Carotid sinus syndrome is a set of signs and symptoms with which the patient presents himself to the physician, while a hypersensitive carotid sinus is a sign which is elicited by the physician and which may or may not be related to the patient's complaints. It has been observed in this series, as others have noted too, that patients with CVI are more likely to have increased carotid sinus sensitivity; however, in reviewing the cases in this series, I have not been impressed that there is much of a problem in most instances in differentiating cases of carotid sinus syndrome from cases of CVI with hypersensitive carotid sinus (with or without transient episodes). Hence, though this series cannot disprove the idea that carotid sinus hypersensitivity is an important factor in transient episodes of CVI, there is nothing here to substantiate such an idea.

Is the carotid compression test safe? There are reports of hemiplegias or monoplegias due to digital compression of the carotid in testing for carotid sinus sensitivity.[19–23] On the other hand, some authors with considerable experience with this procedure report either that it is safe or that the dangers are minimal.[23,24] The complications seem to be of two sorts: one that occurs immediately, which at least in some cases may be due to the carotid sinus' producing a prolonged asystole and/or a severe drop in blood pressure, and a second type that occurs later—minutes? to hours—which can best be explained by an embolus breaking off from an atheromatous plaque. Hence, the latter type would be due to damage to the arterial wall incurred by the manipulation of the artery.

TABLE 6
RELATIONSHIP OF VAGAL RESPONSE AND TYPE OF CVI EPISODE

Patients with unilateral carotid insufficiency with a definite . . .	*Number of patients*	*Number of patients with vagal response*	*Per cent of patients with vagal response*
Single, nontransient major episode	33	11	33
History of several, transient episodes	11	3	27

Momentary impairment of consciousness and/or minor focal seizures were not rare in this series during compression, although they usually occurred with the more prolonged compression that was performed in the attempt to obtain an ischemic response. Serious side effects did occur twice; these seemed to be due to the second type of complication, that is, embolization.

Case 1. A 66-year-old man had been hospitalized on the Medical Service in June 1957 because of acute myocardial infarction. Since that time, he felt fatigued and complained of "dizzy spells" lasting seconds to minutes, two to three times a month. During these times, he would stagger if walking but did not fall or lose consciousness. Because of these episodes, he was again admitted to the Medical Service on August 5, 1958. No abnormal neurologic findings were recorded. A routine (awake) electroencephalogram was interpreted as normal. Compression of the left carotid artery produced an asystole; hence, prolonged compression for evaluation of the ischemic effects could not be obtained. Compression of the right carotid on 2 occasions produced neither pulse rate nor electroencephalographic changes. The patient was discharged before further electroencephalographic studies could be undertaken. He was ad-

mitted to the Neurology Section on December 23, 1958, because of spontaneous subarachnoid hemorrhage. At this time, minor right hemiparesis was found. On December 29, a left carotid angiogram revealed only a slight narrowing of the artery in the distal syphon; on December 30, a right carotid angiogram revealed narrowing—"probably arteriosclerotic"—of the distal internal carotid and spasm of the anterior and middle cerebral arteries. An electroencephalogram on January 30, 1959, was interpreted as borderline without focus because of "slow alpha;" a carotid compression electroencephalogram—each side was compressed 2 times—again revealed a vagal response on the left. The patient complained of no symptomatic changes, and nothing was noted objectively. On February 5, a repeat carotid compression electroencephalogram—again each side was compressed twice—revealed the same sensitive left carotid sinus; the patient was given 1.2 mg. of atropine subcutaneously, and the carotids were again compressed twice on each side. This time, there was neither pulse rate nor electroencephalographic change although compression on the left made the patient feel "weak" and "passing out" and made the right hand and arm feel "weak and functionless." These changes were transient. About nine hours after the electroencephalogram, the patient complained of the onset of a feeling that the right arm was "clumsy." Examination revealed some clumsiness of fine finger movements on the right which was thought worse than before his last electroencephalogram; sensory examination was normal. This deficit cleared by February 14.

Case 2. A 47-year-old man was admitted to the Medical Service on March 8, 1959, because of chest pain of five hours' duration. He had suffered from episodes of myocardial infarction in 1954, 1955, and November 1958. A diagnosis of peptic ulcer with bleeding was made in 1943. Physical and neurologic examinations were normal. After serial electrocardiograms and serum transaminase studies, it was concluded that he had not suffered a new cardiac insult. During the first two weeks of hospitalization, the patient complained of some giddiness. Roentgenograms of the skull revealed some minor asymmetries of the clinoids. Cerebrospinal fluid examination was normal. On March 25 at 8:30 A.M., a routine (awake) electroencephalogram was obtained which was interpreted as normal; immediately after this, a carotid compression electroencephalogram was obtained. The left carotid artery was compressed first; after fifteen seconds, some theta activity was noted equally well defined in the frontal, posterior, and temporal areas on the left. Because of this, the compression was released within another five seconds. The patient stated that he "felt like [he] was going to pass out." This sensation was limited only to the time of the compression; 2 subsequent compressions on the left and 2 more on the right, each of about thirty seconds, produced neither subjective nor electroencephalographic changes. No significant pulse rate changes were noted. Immediately after the test, examination revealed no differences in the carotid pulsations bilaterally, and no carotid artery bruits were heard. That evening, the patient noted some transient twitching of the right upper lip. Examination revealed mild right hemiparesis and hemihypesthesia; there were normal and equal diastolic ophthalmodynamometric readings. The hemiparesis progressed over the next twenty-four to forty-eight hours, although it never developed into frank hemiplegia. Repeat electroencephalograms without carotid compression were obtained on April 10 and again on April 20; these showed no change since the initial tracing and were again considered normal. By April 18, the hemiparesis had appreciably decreased. He was subsequently transferred to another hospital outside the state in order to be near his home; therefore, his later course is not known.

Hence, serious side effects were experienced in 0.4% of all patients examined in this series and in 1.2% of the patients with CVI; since this test has been used in at least another 75 patients not included in this series and no further difficulties have been encountered, these figures are actually too high. However, it is felt that this procedure is not without risk and therefore should be limited only to those cases in which it can materially aid the diagnosis.

DISCUSSION

It is evident from the results which have been presented that, in patients 59 years of age and younger, there is a higher incidence of carotid sinus sensitivity—at least of the cardioinhibitory type—in patients with CVI than in patients without CVI. We have previously suggested[14] that some patients may have "subclinical" CVI, that is, they have some cerebrovascular disease but not enough to produce the signs and symptoms of CVI. This was based on the increasing frequency of ischemic responses to carotid compression in patients without CVI as they grew older. The frequency of vagal response also increases with age in patients without CVI, and, indeed, after 60, the frequency of vagal response is about the same in patients without CVI as in patients with CVI. Therefore, this adds further weight to the concept of "subclinical" CVI.

The reason for the increase in frequency of carotid sinus sensitivity in patients with CVI is not clear. One possible explanation is that the brain damage secondary to the CVI may

in some fashion alter the carotid sinus reflex. It is difficult, however, to accumulate much evidence to support this particular idea. Since the reflex is via the brain stem, basilar CVI might be expected to alter the reflex; however, of all the various cerebrovascular "trees," basilar CVI is the least likely to be associated with a vagal response, at least in younger patients (Table 7). I have been unable to find any evidence to suggest that stimulation or ablation of any brain area will alter carotid sinus sensitivity, except that reserpine can block the carotid sinus pressor response by acting at the brain stem level.[25]

It is difficult to find any examples of disease in some organ altering the sensitivity of the carotid sinus directly except by decreasing systemic blood pressure or in some other fashion producing generalized bodily change. That coronary artery disease is often associated with carotid sinus hypersensitivity has already been commented upon; too, biliary tract disease has been reported to be associated with an increase in carotid sinus sensitivity.[26] The mechanisms involved are apparently unknown, but it could certainly be suggested that at least some of the patients with coronary artery and biliary tract disease might have carotid artery or "subclinical" carotid artery insufficiency, and the mechanism for carotid artery insufficiency and the mechanism for carotid sinus hypersensitivity are then the same as that associated with coronary artery insufficiency. The course of coronary artery disease and the course of carotid artery disease do not run parallel, at least in large series of patients,[27,28] since the former is more common in younger patients and the latter in older patients; hence, one would not expect atheromatous carotid disease to be the only explanation of hypersensitive carotid sinus effect in all patients with coronary artery disease. Braun and Samet[29] demonstrated an increase in the effect of vagal stimulation on cats' cardiac rate by ligation of the left coronary artery; this offers another possible explanation for the apparent increase in carotid sinus sensitivity associated with coronary artery disease, that is, the efferent limb of the reflex may be altered and, hence, the reflex activity changed without actual involvement of the carotid sinus. The well-known action of digitalis of increasing carotid sinus sensitivity might also work through its effect on the vagus[30] and, hence, cannot be taken as evidence of alteration of the carotid sinus directly. There is a very long list of other drugs, hormones, chemicals,[31] and physical states[32,33] which have been reported to either increase or decrease carotid sinus sensitivity; as far as I can ascertain, no good evidence has been advanced that any of these agents alter carotid sinus sensitivity by acting primarily on some other bodily organ, which then alters the carotid sinus without also changing blood pressure or metabolism or having some kind of generalized effect. Ergotamine may be somewhat of an exception.[4] Therefore, any evidence of a distant organ, for example, the brain, altering the effect of the carotid sinus itself is meager at best.

TABLE 7
RELATIONSHIP OF VAGAL RESPONSE TO TYPE OF CVI

	Vagal response	*Total patients*	*% vagal response*
No CVI	9	185	5
Unilateral carotid CVI	12	27	45
Bilateral carotid CVI	4	9	45
Basilar CVI	1	7	14

The other possible mechanism to explain the increased carotid sinus sensitivity in patients with CVI is that there is some local alteration at the carotid sinus; for this, there is better evidence. The carotid sinus area is a site of predilection for atheromatous changes.[34,35] In younger patients, the group having the fewest vagal responses were those with basilar "tree" insufficiency, that is, where the pathology was away from the carotid; perhaps a vagal response in any of the patients with basilar "tree" insufficiency merely represents a deficiency in our diagnostic acumen, since it is so common to have some degree of carotid artery disease associated with basilar artery disease.[36] Also, there is some evidence from surgical ligation of the internal carotid artery in human beings that such an induced type of insufficiency may of itself produce a sensitive carotid sinus.[37,38]

If the vagal response in patients with CVI is indeed due to local changes at the carotid

sinus, 2 further explanations have been offered as to why these patients' carotid sinuses are unusually sensitive. First, because of the local disease, there may be some deformity of the sinus area; Heymans and Neil,[4] in summing up the literature, state that "the [sinus] nerve endings [in the carotid artery wall] are after all three dimensional and it is equally likely that they can be distorted (and hence stimulated) by longitudinal stretching or indeed by any mode of deformation or distortion." Second, the atheromatous changes (or in the case of "pulseless disease," the "cicatricial tissue around the carotid sinus"[39]) offer a more rigid surface so that digital compression can be better transmitted mechanically.[4,40] The inability in this series to confirm the presence of a "carotid sinus syndrome" in contrast to "carotid sinus hypersensitivity" in patients with CVI suggests that the sinus may indeed not be more irritable than normal; that is, local atheromatous deformity of the artery has not led to increased irritability of the carotid sinus, but that compression of the sinus can now more easily elicit a reflex. Therefore, the idea that increased mechanical transmission of the digital pressure seems better able to explain the results obtained, although one explanation does not entirely exclude the other.

Hence, in light of the studies of others and the material presented here, the increased frequency of vagal response seen in patients with CVI can best be interpreted as a manifestation of local atheromatous changes at the carotid sinus which make eliciting the carotid sinus reflex by digital compression an easier task than in patients without CVI. That other factors may play some role cannot be ruled out.

Previously,[14] we were able to confirm the findings of others that patients with CVI are more likely to have manifestations of cerebral ischemia when their carotids are occluded by digital compression than are patients without CVI. We avoided getting involved with the problem of whether this was some sort of reflex to cerebral vessels via the carotid sinus or indeed, what may be a good possibility at least in a few cases, whether this is due to a combination of a carotid sinus effect and carotid artery occlusion. Regardless of the mechanism for the production of a local cerebral ischemia in some patients but not others, an ischemic response must be due to less collateral circulation to this local area in those patients who have signs and symptoms in contrast to those who do not. Hence, the ischemic response, when obtained, and regardless of the mechanism, is a manifestation of less than "normal" collateral circulation. In other words, an ischemic response due to compression of the carotid is a measure of cerebral collateral circulation. In contrast to this has been the not original proposal offered in this paper that the vagal response from carotid compression is a measure of the "hardness" of the carotid artery at the carotid sinus, that is, the presence of some disease process in this area. Therefore, if this is so, the 2 possible types of responses that can be obtained by digital compression of the carotid are measures of 2 different factors, local carotid artery disease (the vagal response) and the degree of impairment of cerebral collateral circulation (the ischemic response). Proof for this statement would be the ability to obtain the ischemic response from compression of the "good" carotid only and the vagal response from the compression of the "diseased" carotid only. Review of the results offered here (Table 3) does not show this; however, this really does not disprove the hypothesis since the basis for diagnosis was totally inadequate to quantitate and probably in many cases even to identify the presence of cerebrovascular disease (in contrast to cerebrovascular insufficiency) in all 3 "trees" in any given patient. In fact, the presence of "subclinical" CVI implies that many of the patients have some degree of cerebrovascular disease without diagnosable cerebrovascular insufficiency. For example, how much left carotid artery and basilar artery disease without the clinical syndrome of CVI there may have been in a patient with right carotid "tree" CVI cannot be easily determined, even though it may be very apparent that all his signs and symptoms are due to his right carotid insufficiency. It is hoped that eventually an adequately large series of patients with unilateral carotid "tree" insufficiency without disease of the other carotid artery and its "tree" and without disease of the basilar artery and its "tree"—proved by angiography or, better, at autopsy—who have been examined

with digital carotid compression can be accumulated. Until such a series is obtained, the suggestion is offered that the 2 types of responses from digital carotid compression—a vagal response and an ischemic response—are manifestations of 2 different factors, that is, rigidity of the carotid wall and decrease in cerebral collateral circulation.

CONCLUSIONS

Unilateral digital compression of the carotid was performed on 166 patients with clinical evidence of cerebrovascular insufficiency and 280 patients without clinical evidence of CVI in order to evaluate the presence of a "cardioinhibitory" carotid sinus response (vagal response) as a diagnostic sign in patients with CVI. The following conclusions can be drawn from this study:

1. Increased carotid sinus sensitivity occurs significantly more often in patients with CVI than in patients without CVI only if the patients are under the age of 60; therefore, a sensitive carotid sinus may be of value in the clinical diagnosis of CVI in patients under the age of 60 but not in older patients.

2. A unilateral sensitive carotid sinus usually but by no means invariably is present on the side opposite to unilateral carotid "tree" insufficiency.

3. In patients under 60, the presence of both a vagal response due to carotid sinus stimulation and an ischemic response (using the electroencephalogram as an end point) due to occlusion of the carotid artery is better evidence of CVI than the presence of only one or the other of these responses.

4. A sensitive carotid sinus found in a patient with CVI may be independent of any evidence of atherosclerosis elsewhere in the body. However, if a patient has coronary artery insufficiency, finding a sensitive carotid sinus decreases the value of this sign in making a diagnosis of CVI. This works in reverse, too, that is, if the patient has CVI, finding a sensitive carotid sinus decreases the use of this sign in making a diagnosis of coronary artery disease.

No evidence was obtained from this study that a hypersensitive carotid sinus plays an important role in the transient episodes seen in some patients with CVI.

Digital carotid compression is not without risk. The following suggestions are offered:

1. A sensitive carotid sinus in a patient without cerebrovascular disease may be evidence of "subclinical" CVI, that is, some degree of cerebrovascular disease but not enough disease to produce the signs and symptoms of cerebrovascular insufficiency.

2. The apparent increase in carotid sinus sensitivity found in patients with CVI may not represent an actual increase in the sensitivity of this organ, but, rather, it may only be that it is easier to elicit this reflex by digital compression because of atheromatous changes in the carotid artery. It would follow then that the 2 possible types of responses that can be elicited by digital compression of the carotid are due to 2 different factors: the vagal response of the carotid sinus may be a manifestation of atheromatous changes at the carotid bifurcation, while the ischemic response is a measure of cerebral collateral circulation.

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Increased cerebrovascular permeability after repeated electroshocks

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In 1957, Rozdilsky and Olszewski[1] showed that repeated electroshocks increased the permeability of cerebral blood vessels to protein molecules. This increase was more intense in the gray than in the white matter and was particularly pronounced in the thalamus. In order to study the mechanism responsible for this increased permeability, additional experiments have been carried out in our laboratory. The results of these experiments are reported in the present paper.

MATERIAL AND METHODS

Experiments were performed on 14 cats and 7 rabbits of both sexes and mixed breed. Radioactive iodinated bovine albumin obtained commercially from C. Frost, Montreal, was used as an indicator of changes in the cerebrovascular permeability. According to the manufacturer, the concentration of albumin in the solution was 2% and not more than 2% of radioactivity was due to unbound iodine. The volume of the solution for intravenous injection varied from 4 to 7 cc., corresponding to an approximate dose of 0.5 mc. per kilogram of body weight. Electrodes for administration of electroshocks were implanted one day before the actual experiment. The animal was anesthetized lightly with ether; 2 thin brass disks about 1 cm. in diameter—with soldered wires leading from the disks—were inserted between the epicranial tissues and the skull through small skin incisions, 1 on each side of the parietal region. The skin was sutured, and the animals recovered quickly from the anesthetic. On the following day, the wires protruding from the skin were connected to the output of a Variac and the electroshocks were induced in the animal by manually pressing the switch for approximately half a second. The voltage was 80 volts for cats and 60 to 70 volts for rabbits.

The radioactive albumin solution was injected after electroshocks were begun. In experiments in which no electroshocks were administered, the radioactive albumin was injected before the actual experimental procedure was started but after the animal was prepared by anesthesia, thoracotomy, tracheotomy, or any of other introductory steps.

The changes of permeability were studied by autoradiographic technic, using the apposition method with no screen x-ray film as described previously.[2] The animals were killed by exchange perfusion with 6% dextran in saline to remove radioactive blood from the lumina of the vessels. The perfusion was continued with a fixative of 30% ethyl alcohol in 10% formalin. The brains were removed and fixed overnight in the same fixative. Frozen sections 50 μ thick were cut for autoradiography. After the exposure, the sections were stained by the Nissl method.

Autoradiographs which did not show radioactivity of distribution different from that of control untreated animals will be referred to as negative.

RESULTS

Since the experiments of Rozdilsky and Olszewski were performed on cats, we wanted to find out whether repeated electroshocks would produce a similar pattern of increased permeability in another species; 1 rabbit was given 55 electroshocks and 2 rabbits 40 electroshocks each. The resulting increase of permeability is illustrated in Figure 1. In all 3 animals, there was an intense darkening of the

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emulsion over the thalamus and the hypothalamic area extending laterally into the region of the amygdaloid nuclei. The lateral geniculate bodies stood out very conspicuously. The hippocampi were moderately darkened, but the remaining cerebral cortex was spared. The meninges were outlined as a fine dark line.

During our experimentation, some colleagues expressed the thought that the increased permeability could be due to the direct damage of the brain tissue by the electrical current. To test this assumption, we administered 62 shocks to a cat under Nembutal anesthesia. Only slight twitching of muscles of the head indicating the passage of electrical current was observed, but there was no generalized seizure. Autoradiographs of this experiment were negative.

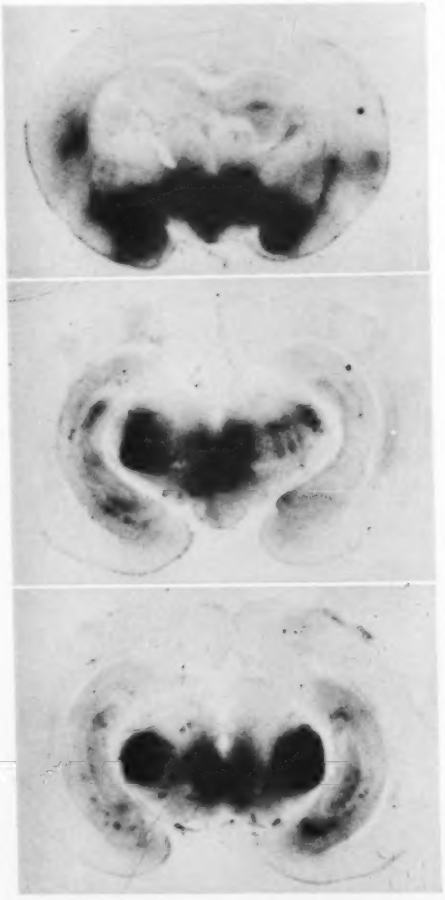

Fig. 1. Autoradiographs of 3 coronal sections of rabbit's brain; 55 electroshocks

The influence of CO_2 on the cerebral permeability was tested in 3 experiments. We felt that, during repeated electroshocks, CO_2 concentration in blood might rise. Furthermore, CO_2 is known as a potent cerebral vasodilator, and vasodilation occurs during convulsive seizures. A cat and 2 rabbits were used in this group of experiments. The animals were placed individually in a tight glass container of about 10 liters' volume, and a constant slow stream of carbogen (5% CO_2 in 95% O_2) was passed through the container. Besides deep and fast respirations, there was no other change in behavior of the animal during its exposure to carbogen. Autoradiographs of all 3 animals were negative.

Dobkin and Olszewski[3] reported that unmodified electroshocks cause significant changes in the blood pressure. To study the influence of changes of the blood pressure on cerebrovascular permeability, 2 groups of experiments were performed. In the first group, the influence of the rise of the pressure was investigated; 2 approaches were used in this group —raising of the pressure without administration of electroshocks, and administration of electroshocks with prevention of the rise of the blood pressure.

First approach. Nembutal was used to anesthetize 3 cats. The chest was opened, and artificial respiration was instituted via tracheotomy. A loop of suture silk folded several times was passed around the descending thoracic aorta. The 2 limbs of the loop were threaded through a glass tube. When the limbs were pulled, the aorta was drawn up by the loop firmly against the lower end of the tube and thus the blood flow was obliterated. After injection of radioactive albumin, this maneuver was repeated sixty times, the pulling being applied for ten to fifteen seconds, each time at five-minute intervals. In 1 cat, the changes of the blood pressure were recorded by connecting 1 carotid artery to a mercury manom-

eter. Each obliteration of the aortic blood flow caused a rise of the systolic blood pressure from the level of about 170 to about 260 mm. Hg. In all these cats, the autoradiographs were negative.

Second approach. In 2 cats, the electroshocks were administered after premedication with chlorpromazine; 1 cat received 0.7 mg. and the other 0.9 mg. of chlorpromazine. They became quiet but reacted to the electric current with the usual vigorous tonic-clonic seizures. Each animal was given 62 electroshocks. The autoradiographs showed a pattern of radioactivity identical to that seen after electroshocks without premedication, though of lesser intensity (Fig. 2).

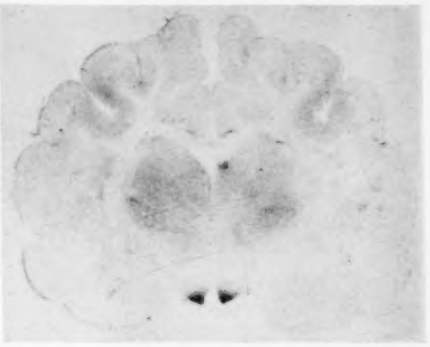

Fig. 2. Autoradiograph of a coronal section of cat's brain; 60 electroshocks after premedication with chlorpromazine

In the second group of experiments, the influence of the fall of blood pressure was investigated; 3 approaches were used—lowering of the blood pressure by stimulating the vagus nerve, lowering of the blood pressure by clamping the ascending aorta, and prevention of the blood pressure from falling during electroshocks by premedication with atropine.

First approach. In 1 cat, the left vagus nerve was exposed under Nembutal anesthesia and was stimulated sixty times with an electric current of 5 volts and 60 cycles for ten to fifteen seconds once every five minutes. The blood pressure was measured through the femoral artery. The stimulation was accompanied by a fall of the blood pressure of about 40 mm. Hg lasting approximately fifteen seconds. Autoradiographs of this experiment were negative.

Second approach. In 2 rabbits and 1 cat under Nembutal anesthesia, the chest was opened and artificial respiration initiated via tracheotomy. The ascending aorta was dissected and enclosed in a loop of the suture silk. The procedure was otherwise identical with that described above. The circulation was interrupted sixty times at five-minute intervals for ten to fifteen seconds each time. The autoradiographs of these animals were all negative.

Third approach. Atropine, 0.8 mg., was given to 2 cats which then received a series of 62 electroshocks. The autoradiographs of these cats showed the pattern of radioactivity typical of that seen after electroshocks without premedication.

In spite of the results of these experiments, we considered that, even if the rise and fall of the blood pressure are not a direct cause of the increased permeability, the blood flow must have a direct relationship to the intensity of radioactivity observed on the autoradiograph. That such is indeed the case was proved in an experiment in which one common carotid artery was ligated in the neck the day before the administration of electroshocks. On the side of ligation, the radioactivity was less intense in the thalamus (Fig. 3).

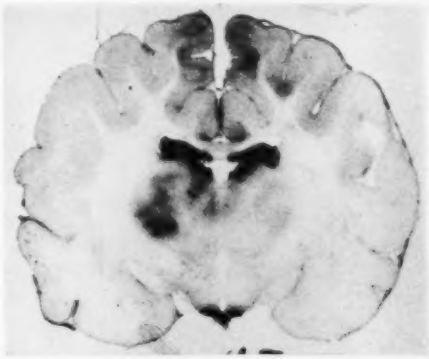

Fig. 3. Autoradiograph of a coronal section of cat's brain; 60 electroshocks with ligation of carotid artery on right side

In a final series of experiments, the electro-

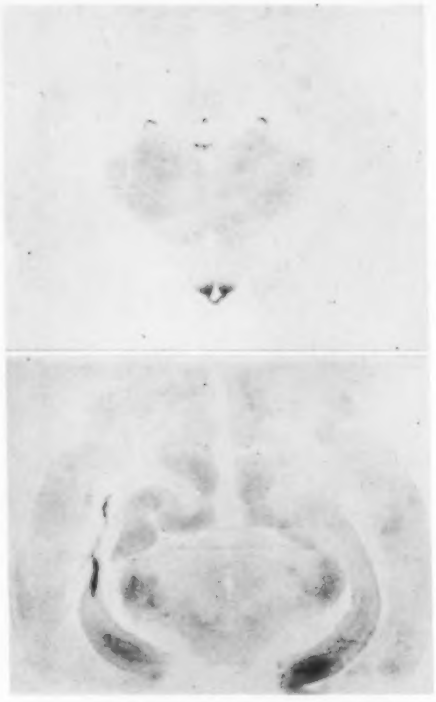

Fig. 4. Autoradiographs of 2 coronal sections from 2 brains of cats; 60 electroshocks after premedication with Flaxedil

shocks were administered after premedication with Flaxedil, a synthetic curare-like drug. Under ether anesthesia, 2 cats were tracheotomized. Procaine was injected around the wound. After the discontinuation of ether but before the onset of electroshocks, Flaxedil was injected at a dosage of 2 mg. per kilogram of body weight. As soon as spontaneous respirations stopped, the artificial respiration was started. In 1 cat, the blood pressure was recorded by connecting the left femoral artery to a mercury manometer. The wound around the femoral artery was injected with procaine. The systemic blood pressure was 80 mm. Hg after the injection of Flaxedil but increased to about 120 mm. after the electroshocks. The only response to the shock was slight contractions of the facial musculature in direct response to the current. Autoradiographs of these 2 animals showed a pattern of radioactivity similar to that seen after nonpremedicated electroshocks, though the intensity was rather low (Fig. 4).

DISCUSSION

As has been mentioned by Rozdilsky and Olszewski, there are two main problems related to the increased vascular permeability observed after repeated electroshocks. The one is the question of differential distribution of radioactivity; the other is the actual mechanism responsible for the increased permeability. The experiments reported in this paper do not add much additional information in regard to the first question. In the rabbit, the distribution of radioactivity was slightly different from that observed in the cat, but the over-all tendency of a greater change in the gray than in the white matter was the same.

Rozdilsky and Olszewski considered that the particularly intense radioactivity in the thalamus might be a reflection of the active part played by the thalamus in the mechanism of epileptic seizure. The report by Sokoloff[4] on the cerebral blood flow which appeared in the meantime suggests to us an alternative more likely explicable. We were struck by the similarity between Sokoloff's autoradiographs, which reflect the cerebral blood flow, and ours, which indicate increased permeability after electroshocks. We suggest, therefore, that repeated electroshocks produce a diffuse increase of permeability which is more or less constant per surface unit of the capillary wall. The autoradiographic pattern reflecting the increased permeability would depend mainly on two factors: the density of the capillary network and the blood flow in this network. The dependence of the intensity of the autoradiographic pattern on the blood flow was demonstrated in our experiment with ligation of one carotid artery, in which the radioactivity of the brain was less pronounced on the side of ligation. It is also possible that the weak autoradiographic pattern seen in experiments with chlorpromazine and Flaxedil was due to the low blood flow and not to any specific action of the drug.

The second question which was mentioned at the beginning of the discussion was an-

swered partly by the results of our other experiments. There seems to be no question that the increased permeability after repeated electroshocks is caused either directly by the electrical current or directly or indirectly by the higher concentration of CO_2 in the blood. It seems also that the variations of the blood pressure are not responsible for the changes in the vascular permeability observed in our experiments. We do not intend to make a general statement that variations in the blood pressure do not influence vascular permeability. Our statement is applicable to our specific experiments only. Perhaps the most significant was the observation of increased vascular permeability after electroshocks and premedication with Flaxedil. It indicated that increased permeability is not dependent on over-all metabolic changes related to muscular contractions or changes in respirations but rather on local phenomena in the nervous tissue. The negative results obtained after the electroshocks administered to the anesthetized animal suggest that these phenomena may be related to neuronal activity occurring during the seizures. Further work is required to clarify this point.

SUMMARY

Cerebrovascular permeability was studied in 14 cats and 7 rabbits. Radioactive iodinated bovine albumin and autoradiographic technic were used. The purpose of these experiments was to elucidate the mechanism responsible for the increase of permeability during repeated electroshocks.

In the rabbit, the cerebrovascular permeability increases in a manner similar to that observed in the cat, with only minor differences in localization.

General anesthesia by Nembutal prevents the increase of permeability.

The theory is proposed that the pattern of radioactivity seen after electroshocks is due to differences in the vascularity and particularly in the blood flow through various parts of the central nervous system.

The high concentration of CO_2 in the blood and variations of the blood pressure occurring during electroshocks are not the cause of the increased permeability of cerebral blood vessels.

It is possible that the increased permeability is related to increased neuronal activity during electroshocks.

The assistance of Abbott Laboratories Limited in providing dextran free of charge is acknowledged.

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Effect of prolonged hypoxia on cerebrospinal fluid and plasma activity of GOT and LDH

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THE TRANSFER of the enzymes glutamic oxalacetic transaminase (GOT) and lactic dehydrogenase (LDH) from plasma to cerebrospinal fluid is prevented normally by the blood–cerebrospinal fluid barrier.[1–4] Elevated cerebrospinal fluid enzyme activity has been reported in dogs with experimental cerebral infarction and in human beings with cerebrovascular accidents and convulsions.[5–9]

In an earlier investigation, we reported increased permeability of the blood–cerebrospinal fluid barrier to albumin I^{131} after prolonged hypoxia.[10] The present study is concerned with the effect of prolonged hypoxia on the cerebrospinal fluid and plasma GOT and LDH activity in puppies as related to increased permeability of the blood–cerebrospinal fluid barrier.

METHOD

A total of 53 normal mongrel puppies aged 2 to 3 months was studied; 37 puppies were subjected to barometric pressures of 258.1 mm. Hg (27,000 ft. altitude) to 162.4 mm. Hg (37,000 ft. altitude) in a Smith-Jones pressure chamber for three hours, arriving at the respective altitudes in about twenty minutes. Studies by other workers have shown that, at altitudes of 25,000 and 35,000 ft., arterial blood oxygen saturations are approximately 45 and 10%, respectively.[11] Pentobarbital sodium (25 mg. per kilogram) was administered intraperitoneally or intravenously as an anesthetic at the termination of the experimental period so that cisternal punctures could be performed. Only 1 cisternal puncture was performed on this group of puppies. An additional 6 puppies were followed with repeat cisternal taps at varying intervals of one to three days over a period of one week after the initial hypoxia.

Heparinized blood samples and 2 cc. of cisternal fluid were obtained at the termination of the hypoxic period. Plasma was separated from erythrocytes after centrifugation at 3,000 rpm for five minutes. Specimens were stored frozen, and enzyme determinations were performed within a week. Cisternal fluid containing erythrocytes was centrifuged and separated immediately to avoid high values from hemolysis. Plasma specimens showing hemolysis were discarded.

Control plasma and cisternal fluid specimens were obtained from 16 puppies which were treated exactly as the experimental group omitting hypoxia.

GOT and LDH activity was measured using the methods described by Karmen[12] for GOT and Wroblewski and LaDue[13] for LDH. All determinations were performed at approximately 25° C. Concentration ratios of the cerebrospinal fluid to plasma enzyme activity were calculated in each case.

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Radioactive iodinated human serum albumin in doses of 11 μc. per kilogram of body weight was given intravenously to all experimental and control puppies to evaluate the permeability of the blood–cerebrospinal fluid barrier by measuring the rate of passage of isotope from blood to cerebrospinal fluid. In the experimental group, the isotope was injected just before the institution of hypoxia. In 32 puppies, cerebrospinal fluid and plasma in samples of 1 cc. and 0.1 cc. made up to 1 cc. with physiologic saline, respectively, were measured in a well-type scintillation counter and recorded as counts per cubic centimeter per minute. (Cisternal fluid containing more than 30 erythrocytes per cubic millimeter was discarded.) Concentration ratios of cerebrospinal fluid radioactivity to plasma radioactivity were calculated from these readings. After precipitation of the protein in a sampling of specimens obtained, no significant radioactivity was found in the filtrate. Since metabolic degradation of the labeled albumin I^{131} occurs at the rate of 9 to 13% per day,[14] the maximum amount degraded over the three-hour experimental period would be less than 2%. Significant contamination of labeled albumin with nonprotein-bound I^{131} therefore would not be anticipated.

RESULTS

The average activity of cerebrospinal fluid GOT was 5 times greater in the hypoxic group than in the control series, and the average cerebrospinal fluid LDH activity was 3 times greater (see table). The average change in the experimental group showed an increase of 410.3% in cerebrospinal fluid GOT activity and an increase of 207.8% in cerebrospinal fluid LDH activity. Only slight increase was observed in this hypoxic group in both GOT and LDH plasma activities. Therefore, when concentration ratios (cisternal fluid enzyme activity: plasma enzyme activity) were calculated in these cases (30), a definite increase in GOT concentration ratios was observed (+261.4%) with a less marked but still definite increase in LDH concentration ratios (+92.9%).

As reported in a previous study,[10] a marked increase in albumin I^{131} concentration ratio (cisternal fluid radioactivity: plasma radioactivity) occurs with hypoxia maintained for an hour or longer, indicating increased permeability of the blood–cerebrospinal fluid barrier. The present series of puppies with three hours of continued hypoxia showed similar results (see figure). When hypoxia was continued for longer than one hour, 96% of the puppies showed concentration ratios greater than those obtained in the control series. The average increase in concentration ratios was approximately 5 times that in the controls.

DISCUSSION

Massive quantities of GOT given intravenously will not produce an increase in the cerebrospinal fluid activity nor will the increased GOT plasma activity associated with hepatic injury be reflected by an increase in the cerebrospinal fluid activity.[2] This indicates that the blood–cerebrospinal fluid barrier prevents the transfer of these enzymes from the plasma to the cerebrospinal fluid.

In experimental cerebral infarction or cerebrovascular accidents in human beings, the

GOT AND LDH ACTIVITY AFTER THREE-HOUR HYPOXIA

	GOT (unit per cc. per minute)			LDH (unit per cc. per minute)		
	Number of cases	*Average ± standard deviation*	*Range*	*Number of cases*	*Average ± standard deviation*	*Range*
Control						
Cerebrospinal fluid	16	2.04 ± 0.23	1.0– 3.25	14	4.46 ± 1.77	1.1– 6.7
Plasma	13	15.3 ± 12.30	8.7– 56.0	10	332.50 ± 83.60	150.0–1,030
Ratio × 10^{-3}	13	179.5 ± 86.40	72.7–309.5	10	21.70 ± 12.46	7.0– 37.0
Hypoxia						
Cerebrospinal fluid	37	10.4 ± 5.46	2.0– 29.0	37	13.73 ± 11.77	3.3– 50.0
Plasma	30	21.6 ± 12.70	5.0– 60.0	30	464.00 ± 367.0	110.0–1,640
Ratio × 10^{-3}	30	648.7 ± 521	141.2–2,900	30	41.85 ± 34.35	6.0–129.7

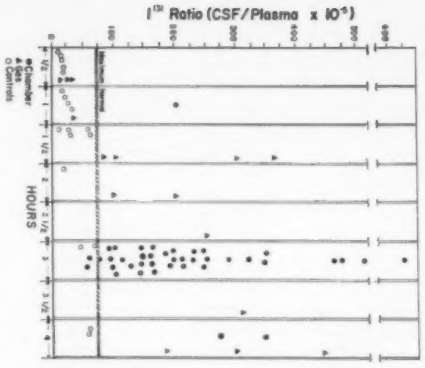
increase in cerebrospinal fluid activity is probably due to cerebral cell necrosis.[1,3,5] Miyazaki[9] has speculated that the increase in cerebrospinal fluid GOT activity observed in patients with convulsive disorders is due to alterations in cerebral cell membrane permeability. Wroblewski and associates[15] have shown that alterations in body fluid enzyme may occur in the absence of tissue necrosis.

In our recent studies on experimental convulsions in puppies,[16] there was a marked increase in cerebrospinal fluid GOT and LDH activity with a corresponding similar increase in the plasma enzyme activity. (The increased muscular activity during the prolonged seizure was probably responsible for elevation of the blood enzyme activity.) Therefore, the enzyme concentration ratios observed in that series showed essentially no change over those obtained in the controls. These results suggested that increased cerebral cell membrane permeability was a major factor during prolonged seizures.

In the present series of hypoxic puppies, the increases were similar to those observed in our study of newborn infants with suspected intracranial pathology and clinical evidence of hypoxia.[17] The primary difference between the human and animal series related to the more marked elevation of LDH in human beings as opposed to the more prominent increase of GOT in puppies.

The possible explanations for the increase in enzyme content could be [1] cerebral cell necrosis, [2] increased permeability of the blood–cerebrospinal fluid barrier, [3] increased permeability of the cerebral cell membrane, and [4] a combination of these.

Wakim and Fleisher[5] showed that dogs with experimental cerebral infarction do not show maximum elevation of cerebrospinal fluid enzyme activity until one hundred hours after injury. It would therefore be difficult to accept actual cerebral tissue necrosis as contributing significantly to the increase in cerebrospinal fluid enzyme activity observed after hypoxia, since follow-up studies with repeat cisternal taps over a period of one week in 6 puppies showed the maximum cerebrospinal fluid activity of GOT and LDH immediately after cessation of hypoxia with a subsequent decrease as early as twenty-four hours later.



Concentration ratios (cerebrospinal fluid : plasma) albumin I^{131} as a function of time in hypoxic and control puppies. Hypoxia was produced by either a pressure chamber or gas mixture (varying amounts of $N_2 + O_2$). Each point indicates the ratio in a single animal.

The increase in albumin I^{131} concentration ratios obtained in the present series indicates a marked increase in permeability of the blood–cerebrospinal fluid barrier to albumin with prolonged hypoxia. Since GOT and LDH do not penetrate the normal blood–cerebrospinal fluid barrier, the marked increase observed in cerebrospinal fluid : plasma enzyme ratios with hypoxia can be interpreted as also indicating some increase in permeability of the barrier. The minimal change in the blood enzyme activity with a marked increase in the cerebrospinal fluid enzyme activity could also indicate that increased cerebral cell membrane permeability plays a role in the results obtained.

Considering the aforementioned factors, increased permeability of the blood–cerebrospinal fluid barrier appears to play a major role in the increased enzyme concentration ratios observed in the hypoxic puppies with probably increased cerebral cell membrane permeability as an additional factor.

SUMMARY

The effect of prolonged hypoxia on cerebrospinal fluid and plasma GOT and LDH activity was studied in 37 puppies.

The average activity of cerebrospinal fluid

GOT was 5 times greater in the hypoxic puppies than in the controls; the LDH activity was 3 times greater. Negligible increases in plasma activity of both enzymes were observed.

Cisternal fluid radioactivity : plasma radioactivity concentration ratios of albumin I^{131} were measured concomitantly with the enzyme determinations and demonstrated increased permeability of the blood–cerebrospinal fluid barrier to albumin.

Cisternal fluid : plasma GOT and LDH concentration ratios were also definitely increased in the hypoxic series, suggesting that there is increased permeability of the blood–cerebrospinal fluid barrier to these enzymes after prolonged hypoxia rather than actual cerebral cell necrosis. Increased cerebral cell membrane permeability may be an additional factor.

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CO_2 narcosis

An experimental study

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In recent years, retention of endogenous carbon dioxide (CO_2) within the body has become recognized as a cause of neurologic signs such as headache, mental obtundity, confusion, coma, tremor, myoclonic jerks, papilledema, increased intracranial pressure, and electroencephalographic changes.[1–11] The narcotic effects of inhalation of CO_2 in high concentration have long been known for, in the days before nitrous oxide anesthesia, attempts were made to use it as a general anesthetic agent.[5] Electroencephalographic changes due to CO_2 retention consist of an increase in frequency before narcosis followed by progressive slowing, with or without increased amplitude and occasional spike and sharp wave activity.[7–11] If progressive CO_2 retention continues, eventually decreased amplitude with suppression of electroencephalographic activity results.

CO_2 narcosis is usually encountered in patients with chronic pulmonary insufficiency or hypoventilation, but CO_2 retention within the brain may occur due to cerebral circulatory impairment,[12] particularly when the venous outflow from the brain is obstructed. Thus, CO_2 accumulation within the brain may be a factor in the electroencephalographic slowing that sometimes follows clamping of the superior vena cava during open heart surgery.[13]

It is apparent from review of previous clinical and experimental investigations of carbon dioxide narcosis that certain aspects of the problem remain enigmatic or at least unproved. It is well known that hypercapnia is accompanied by respiratory acidosis, but it is also known that high levels of arterial pCO_2 and hydrogen ion concentration may be tolerated by some individuals without clinical or electroencephalographic change.[2,14]

Until a better understanding of the pathogenesis of CO_2 narcosis is achieved, it is unlikely that treatment will be rational or satisfactory. Some of the questions concerning CO_2 narcosis that have been investigated in the present study are listed below.

1] In what manner does CO_2 in high concentration exert a depressant action on the central nervous system?

2] Why is there poor correlation between arterial pCO_2 or *p*H levels and the severity of cerebral symptoms and electroencephalographic change?

3] What effects result from the administration of acetazoleamide (Diamox), sodium bicarbonate, and CO_2-binding agents such as tris(hydroxymethyl)aminomethane (THAM) during CO_2 retention?

4] What mechanisms may account for adaptation or acclimatization to prolonged high levels of CO_2?

5] What mechanisms may account for differences in individual susceptibility to CO_2 narcosis?

Methods

Experiments have been performed on 13 monkeys (Macaca rhesus) and 4 cats weighing between 3 to 5 kg. Operative exposures of all

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types were made under general anesthesia with ether or Nembutal. Tracheostomy was routinely performed. In the majority of experiments, in order to avoid the effects of general anesthetic agents on the electroencephalogram, all operative exposures were made under ether anesthesia supplemented by careful regional anesthesia of all operative sites with Xylocaine and immobilization with d-tubocurarine. This permitted electroencephalographic recording without the tracings being affected by general anesthetic agents, so that any effect of CO_2 could be readily recognized. All recordings were made with 12-channel polygraphs manufactured by Offner, Inc., Chicago, (Type R or Type D) or Grass Instrument Co., Quincy, Mass., (Model 5 polygraph). The polygraph was usually operated at slow speed to record the slow metabolic changes, although occasional samples of record were also made at conventional electroencephalographic speeds. Bipolar electroencephalogram was recorded from 2 phonograph needles inserted through the skull to the dura in such a manner that measurements of cortical blood flow and metabolism were recorded from the same area. The arterial blood pressure was recorded continuously by means of a Statham pressure transducer and the alveolar CO_2 by a Liston-Becker infrared analyzer.

In most of the animals, artificial respiration was continuously maintained at constant rate and stroke volume by a mechanical respirator. Measurements of alveolar CO_2 ($PACO_2$) were continuously drawn through the Liston-Becker CO_2 analyzer by means of a constant-flow suction pump. In the few experiments in which Nembutal anesthesia was used, artificial respiration was not necessary but $PACO_2$ was continuously monitored.

In all preparations, one carotid artery was ligated so that comparison of the effects of CO_2 narcosis on one hemisphere rendered relatively ischemic could be compared to the opposite one having normal blood flow.

After records of the steady state were made, CO_2 narcosis (as judged by electroencephalographic change, abolition of any movement present, and the occasional appearance of myoclonic jerks) was induced by inhalation of gas mixtures having the following compositions: 50% CO_2 and 50% oxygen; 35% CO_2 and 65% oxygen; 20% CO_2 and 80% air. The gas was administered by thrusting a rubber delivery tube, without sealing it, into the inlet of the respirator or tracheotomy tube. The gas mixture was therefore breathed through an open system, and hence the $PACO_2$ could be controlled at will by changing the rate of delivery of the CO_2 mixture.

Continuous measurement of arterial pO_2 (PaO_2), pCO_2 ($PaCO_2$), *p*H (a*p*H), and oxygen saturation (SaO_2) were recorded by means of a small catheter forming an arteriovenous shunt between the femoral artery and vein, arranged in such a manner that the arterial blood continuously passed through a manifold containing electrodes for recording pO_2, pCO_2, *p*H, and oxygen saturation of the blood.[15] The SaO_2 was recorded by means of a Waters oximeter cuvette modified for flow-through recording.[15] The PaO_2, $PaCO_2$, and a*p*H were recorded by electrodes similar to those used for concurrent recording of brain tissue pO_2, pCO_2, and *p*H, and the cortical blood flow was recorded with a thermistor, an increase of flow being indicated by a rise in cortical temperature and vice versa. The tissue electrodes were placed on the pial surface of one or both hemispheres between the electroencephalographic electrodes.[12,15]

In brief, the pO_2 electrode consisted of a polarographic anode (silver–silver chloride wire) and cathode (pure platinum wire) sealed into a rubber probe with a 3-mm. flat surface covered by a thin Teflon membrane (12 μ thick) containing a few drops of saline. A potential of 0.7 volts is supplied to the anode by a potentiometer. The membrane permits gases (oxygen) to diffuse rapidly through it but is impermeable to ions. The pO_2 of the tissue or fluid with which the electrode comes into contact rapidly (one to three seconds) reaches equilibrium with the saline within the membrane, and the pO_2 is recorded by the polarograph on the graph. The pCO_2 electrode consists of a small glass *p*H electrode and silver–silver chloride reference electrode immersed in a few drops of 0.0005 N $NaHCO_3$ and surrounded by a Teflon membrane 12 μ thick which permits passage of gases (CO_2) but not of ions. Since CO_2 rapidly enters into solution to form H^+ and HCO_3^-, changes in *p*H are inversely proportional to the log pCO_2

of the tissues or fluid with which the electrode is in contact.[16] When recordings are made of the pCO_2 of the tissues, a *p*H electrode having a sensitive surface that is flat or concave is preferable to a convex electrode. A suitable electrode is manufactured by Radiometer, Inc. (Copenhagen, Denmark). The pCO_2 was recorded by means of Radiometer[22] or Beckman Model N1 *p*H Meters coupled to the polygraph.

The *p*H electrode consisted of a small glass electrode 2 to 3 mm. in diameter, originally designed by the Beckman Company for gastric intubation. In some experiments, *p*H records at the depth of the brain were made with a microglass electrode 200 μ in diameter.[17] The output from this electrode was recorded by means of a Model N1 Beckman meter coupled in series with one channel of the polygraph.

Methods used for calibration of the electrode have been described in detail elsewhere.[12,15] In brief, the tissue electrodes were calibrated in stirred saline solutions of known pO_2, pCO_2, and *p*H placed in water baths maintained at the same temperature as the cortex (34 to

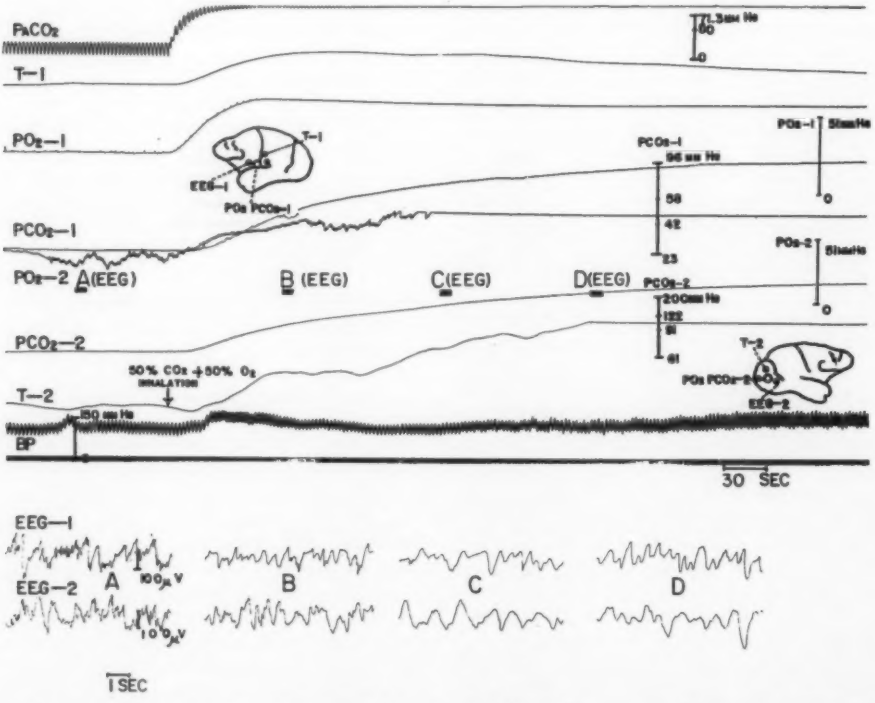

Fig. 1. Continuous polygraphic records at slow speed (upper 9 traces) and concurrent samples of EEG at conventional speed (lower 2 traces) to show metabolic changes during progressive induction of EEG slowing in monkey with left carotid artery ligated. Position of electrodes on brain are shown by 2 brain diagrams. Note that electrodes labeled 1 are from left ischemic hemisphere; those labeled 2 are from right hemisphere. A, B, C, and D indicate points at which EEG was sampled and illustrated. The 2 time bases for polygraph and EEG and calibrations of brain pO_2, pCO_2, ($PACO_2$), and blood pressure (BP) are noted on record. T=cortical blood flow, indicated qualitatively by thermistor beads placed on cortex. Arrow indicates point at which mixture of 50% CO_2 in oxygen was added to inspired air. $PACO_2$ promptly rises with increase of T and cortical pO_2. Brain pCO_2 steadily rises, and EEG slowing is evident when cortical pCO_2 is 120 mm. Hg on the intact hemisphere and 50 mm. Hg on ischemic hemisphere (lower threshold). EEG shows progressive (C) and sustained (D) slowing as brain pCO_2 continues to rise.

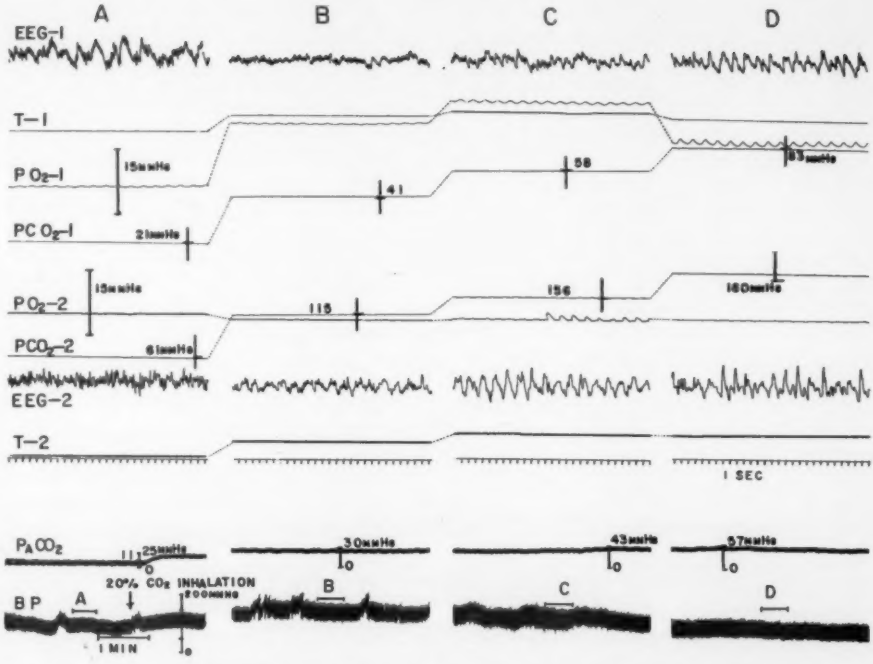

Fig. 2. Monkey, left carotid ligated. A, B, C, and D are samples of continuous polygraphic record, made at faster speed, of concurrent measurements from both cerebral hemispheres. Alveolar CO_2=$PACO_2$. Electrodes marked 1 are recorded from ligated (ischemic) hemisphere; those marked 2 are recorded from intact hemisphere. Arrow marks point where 20% CO_2 in air was added to inspired air. EEG 1 showed slowing before CO_2 breathing. Sample B shows increased cortical blood flow over both hemispheres with rise in oxygen tension of ischemic hemisphere as $PACO_2$ rises. Brain pCO_2 rises over both hemispheres, but, since brain pCO_2 levels were initially higher on intact side, EEG slowing appears more promptly over intact hemisphere. Transient improvement occurs in EEG in ischemic hemisphere before appearance of progressive slowing in records C and D. Note that lower levels of brain pCO_2 are required to produce slowing in ischemic hemisphere. EEG activity in A about 50 to 100 μv in amplitude.

35° C.). The blood electrodes were calibrated by manometric determinations of samples of arterial blood drawn at the beginning of the experiment, before and after hyperventilation and nitrogen breathing.

RESULTS

Brain measurements. Brain pO_2, before CO_2 breathing, as measured with the 3-mm. probe, gave average readings of the tissue on which it rested which often included small arteries and veins. pO_2 levels of brain tissue determined previously with a 1-mm. probe were 10 to 20 mm. Hg.[12,15] In this series of experiments, brain pO_2 levels were often higher, since arteries and veins as well as tissue pO_2 were being recorded. Cortical pCO_2 at the pial surface measured 45 to 60 mm., and the *p*H of the pial surface measured 7.0 to 7.35 units. The *p*H at the depths of cortex as determined with the microelectrodes was usually 0.1 to 0.3 units lower than that at the surface. Brain pCO_2 and hydrogen ion concentration were consistently higher than those of arterial blood, presumably because the metabolism of brain tissue increased tissue CO_2 levels.

Measurements of brain *p*H in areas rendered

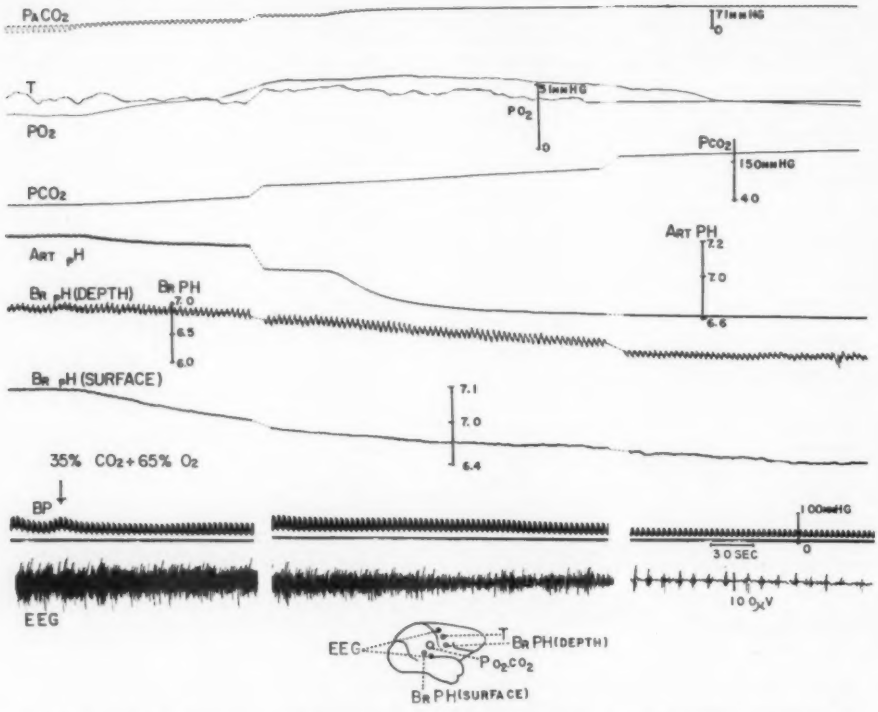

Fig. 3. Samples of continuous polygraphic record of $PACO_2$, cortical T, pO_2, and pCO_2, arterial *p*H (Art *p*H), brain *p*H at depth recorded with microlectrode (Br *p*H [Depth]) brain *p*H at pial surface (Br pH [Surface]), BP, and EEG of monkey during induction of progressive EEG change due to CO_2 narcosis. Electrode positions on brain are indicated by brain diagram. Calibrations are noted on chart. Note that, as *p*H of pial surface decreases to 6.6 (lower at depth), progressive slowing and supression of EEG activity occur. Eventually, as brain tissue acidosis increases, EEG activity is abolished except for bursts of low-voltage spikes.

ischemic by ligation of the carotid artery consistently showed lower *p*H levels than those recorded from the intact hemisphere. In general, in ischemic areas, brain pCO_2 levels were higher (due to diminished CO_2 removal by a sluggish circulation) and brain pO_2 levels were lower. Occasionally, in some experiments, brain pO_2 levels were extremely low due to severe ischemia and electroencephalographic slowing was present before CO_2 breathing. In such experiments, the brain pCO_2 levels were lower than in the intact hemisphere due to reduced cortical metabolism.

Arterial and alveolar measurements. Arterial pO_2 measurements made in these experiments in the steady state were between 70 and 95 mm. Hg. Arterial oxygen saturation measured 85 to 95%. Arterial pCO_2 measured 30 to 45 mm. Hg and arterial *p*H, between 7.17 and 7.42 units. In each of these experiments, the steady state readings remained remarkably constant.

Alveolar pCO_2 measurements were 11 to 30 mm., depending on the respiratory rate, which was usually maintained in a state of moderate hyperventilation.

Effect of inhalation of carbon dioxide in high concentration. When mixtures of air or oxygen having high CO_2 content were mixed with the inspired air, there was an immediate

rise in $PACO_2$ to 60 to 90 mm. Hg. $PACO_2$ levels were maintained constant at these high levels by adjusting the rate of flow of the CO_2 mixture. Arterial *p*H rapidly decreased to 6.6 to 6.8 units, and arterial pCO_2 rose to about 100 mm. Hg. Arterial pO_2 rose no matter whether the CO_2 was administered as a mixture in air or oxygen. When CO_2 was administered as a 20% mixture with air, the rise in pO_2 was accompanied by a decrease in the arterial oxygen saturation, apparently due to the Bohr effect[18] whereby acidity of the blood results in dissociation of oxygen from hemoglobin. When CO_2 was administered as a mixture with oxygen, both SaO_2 and PaO_2 rose because the partial pressure of oxygen in the alveolar air was increased (Fig. 1).

The effects of breathing CO_2 in high concentration on measurements of cortical blood flow and metabolism and the electroencephalogram of the intact cerebral hemisphere were highly consistent. Initially, cortical blood flow was increased since CO_2 has a vasodilator effect on cerebral vessels; later, cortical blood flow tended to decrease since CO_2 in high concentration regularly resulted in a reduction of blood pressure after an initial rise. The cortical pO_2 usually increased after a delay due to the increased pO_2 levels of the blood coupled with the increased cortical blood flow. Brain pCO_2 also increased after a delay, tending to parallel the rising CO_2 levels of the arterial blood. At the beginning of CO_2 inhalation, transient increase in electroencephalographic frequency (similar to cortical activation seen at the beginning of anoxic anoxia) was sometimes seen but may have resulted from metabolic stimulation in the cortex. It appeared that this early activation of the electroencephalogram also may be mediated through an activating reflex from the reticular system resulting from stimulation by CO_2 of the

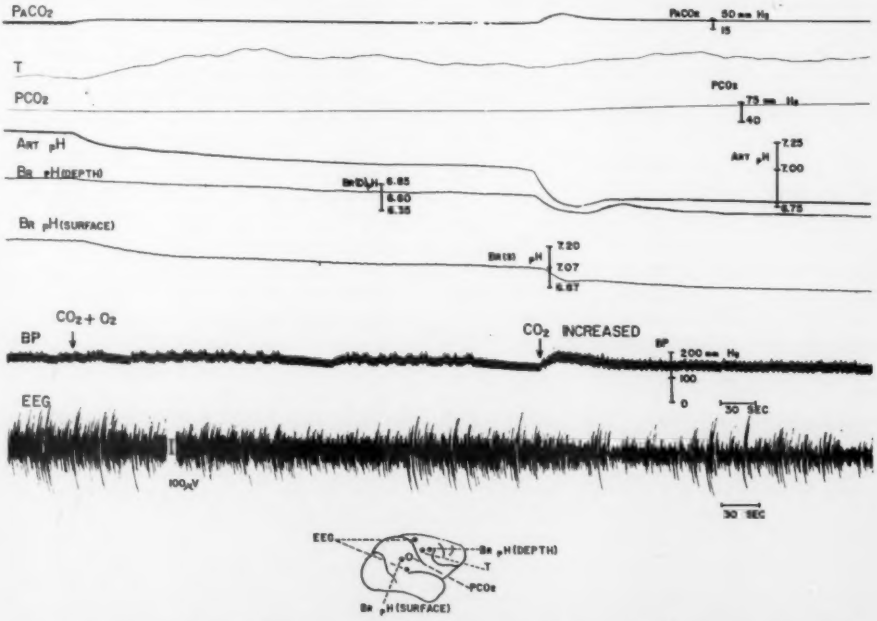

Fig. 4. Continuous polygraphic record during progressive CO_2 narcosis induced by progressively increasing concentration of CO_2 in inspired air. Beginning CO_2 inhalation indicated by first arrow, increase in CO_2 concentration of inspired air (so that brain *p*H threshold is reached) is indicated by second arrow. Some slowing and reduction of EEG amplitude occurred shortly after second arrow.

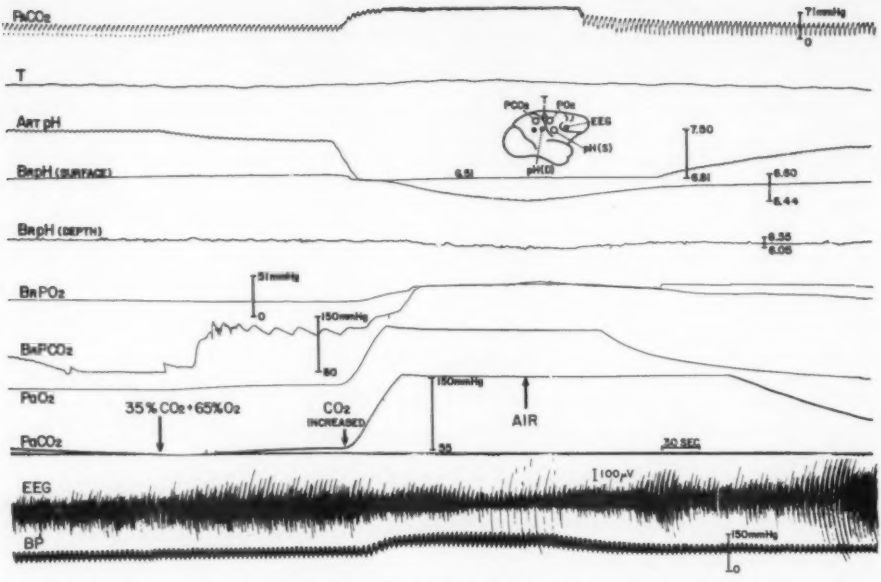

Fig. 5. Monkey exposed to repeated brief episodes of CO_2 narcosis by inhalation of mixture of 35% CO_2 and 65% oxygen added to inspired air at slow rate indicated by first arrow and more rapidly as indicated by second arrow. Brain *p*H is near threshold before CO_2 breathing, and EEG slowing occurs at second arrow when brain *p*H at surface falls below 6.6 *p*H units.

chemoreceptors of the carotid and aortic bodies (Fig. 2).[19]

The brain *p*H became progressively acid as brain pCO_2 steadily increased. In all experiments, the electroencephalogram showed slowing and increased amplitude as the *p*H of the pial surface of the cortex of the monkey was reduced below 6.6 to 6.9 units. Usually, some spike activity appeared in bursts as the electroencephalographic slowing developed. As the brain *p*H fell progressively below 6.6 units, the electroencephalogram frequently slowed to 0.25 to 4 cps (delta activity), often with increase in amplitude and regularly followed by progressive decrease in amplitude of activity until virtual electrical silence supervened save for residual spike discharges in some experiments (Figs. 3 and 4).

If epileptic spike activity was induced in the electroencephalogram before inhalation of CO_2 by application of strychnine or penicillin to the cortex, the spike activity, like the normal electroencephalogram, became suppressed or abolished when the cortical *p*H fell below 6.6 to 6.9 units (Fig. 6). Usually, electroencephalographic changes occurred as brain or arterial pCO_2 rose above 75 to 100 mm. Hg, but, as experimental data accumulated, *p*H appeared to be the critical factor. If the brain was acid before CO_2 breathing (so that the *p*H was between 6.76 and 7.0 units) due to metabolic acidosis or ischemia, CO_2 breathing lowered the *p*H below 6.6 units more promptly, with the appearance of electroencephalographic slowing and eventually suppression in spite of brain pCO_2 levels which remained below 75 mm. Results were comparable in experiments performed on cats except that the electroencephalographic change tended to appear at lower *p*H thresholds (Figs. 5 and 6).

When CO_2 breathing was discontinued, the alveolar and arterial pCO_2 promptly returned to normal levels with a rapid rise of arterial *p*H toward normal. The brain pCO_2 and *p*H returned more slowly toward steady state levels, with a tendency for brain pCO_2 levels

to persist higher than before CO_2 breathing. The electroencephalogram showed restoration of normal rhythm as the brain *p*H rose above 6.7 to 6.9 units (Fig. 7).

Effects of intravenous sodium bicarbonate in CO_2 narcosis. The critical importance of brain *p*H as the factor responsible for the electroencephalographic change in CO_2 narcosis was established by inducing electroencephalographic change by continuous inhalation of CO_2 and then maintaining alveolar CO_2 as well as arterial and brain pCO_2 and *p*H levels constant.

Sodium bicarbonate was then intravenously injected; the arterial *p*H rapidly rose to normal levels, and arterial and brain pCO_2 increased further. The brain usually showed a delayed alkaline shift in spite of the elevated brain pCO_2, and electroencephalographic improvement occurred as the brain became alkaline (Fig. 7).

Electroencephalographic change due to low brain *p*H without CO_2 retention. Since brain *p*H appeared to be the critical factor in CO_2 narcosis, metabolic acidosis was induced by repeated intravenous injections of 3.3 mEq. of acetic acid or 15 mEq. of 1N. hydrochloric acid. When brain *p*H at the pial surface of the monkey was reduced below 6.6 to 6.9 units, electroencephalographic slowing appeared and corresponded to the change in brain *p*H and not to that of the arterial *p*H (which was lowered more transiently). The electroencephalographic change was clearly

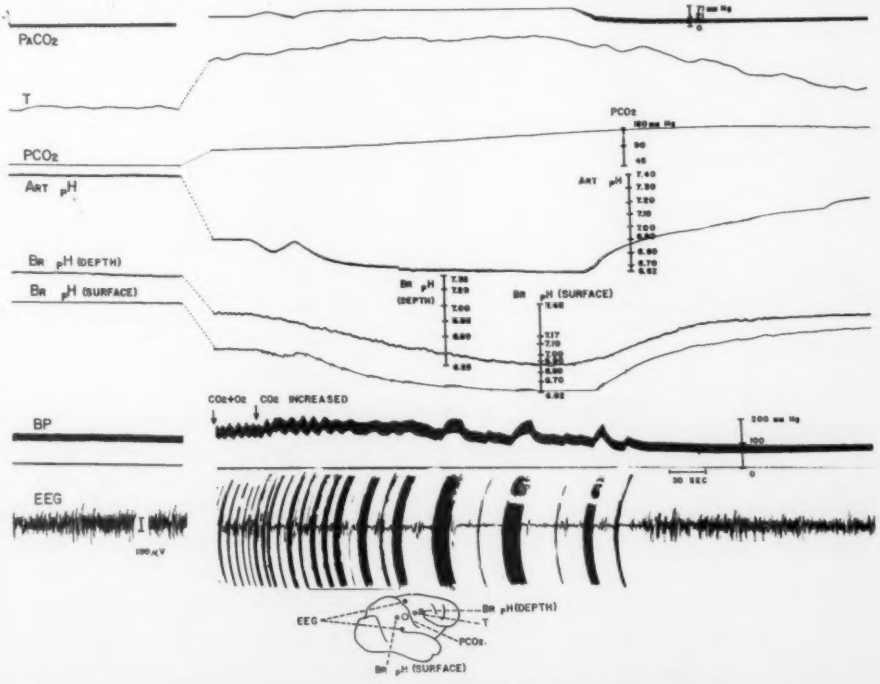

Fig. 6. Samples of polygraphic records made before and during CO_2 narcosis produced in monkey under ether, regional Xylocaine, and d-tubocurarine anesthesia. CO_2 inhalation had begun several minutes before first arrow and was increased at second arrow. This record shows suppression of EEG with appearance of spikes in bursts which become progressively suppressed as brain *p*H is reduced. Possibly, liability to seizure activity was enhanced by use of d-tubocurarine. CO_2 was discontinued, and air breathing was resumed at point where $PACO_2$ decreases. Note that EEG activity improves as brain surface *p*H rises between 6.8 and 6.9 units.

not due to retention of brain pCO_2, since the increase in brain pCO_2 was slight (Fig. 8).

Effect of intravenous THAM during CO_2 narcosis. THAM is an organic buffer base which combines readily with CO_2. Intravenous injections of this material during CO_2 narcosis caused a rapid alkaline shift of the arterial blood and a decrease in $PaCO_2$. Although brief, these chemical changes tended to increase brain *p*H, reduce brain pCO_2, and resulted in some electroencephalographic improvement (Figs. 8 and 9).

Acetazoleamide (Diamox) in CO_2 narcosis. The intravenous administration of 250 mg. of acetazoleamide during CO_2 narcosis resulted in a transient alkaline change in *p*H followed by a gradual and progressive shift in a*p*H to the acid side, presumably because of loss of buffer base by the kidney. Alveolar and brain pCO_2 rose, and brain *p*H decreased further since carbonic anhydrase is inhibited in the erythrocytes and CO_2 transport from the brain by the venous blood is interfered with. The increased acidosis of brain tended to result in electroencephalographic worsening (Fig. 9).

Effects of cerebral ischemia in CO_2 narcosis. In most experiments, the hemisphere rendered ischemic by occlusion of one carotid artery was predisposed to CO_2 narcosis. Before CO_2 inhalation, the ischemic hemisphere regularly showed a brain *p*H lower than that of the intact one. CO_2 breathing thus resulted in a prompter lowering of brain *p*H below the critical level on the ischemic side with the appearance of electrencephalographic slowing lateralized to that side. In 2 experiments, ischemia was so severe that there was little blood flow on the ligated side with low brain

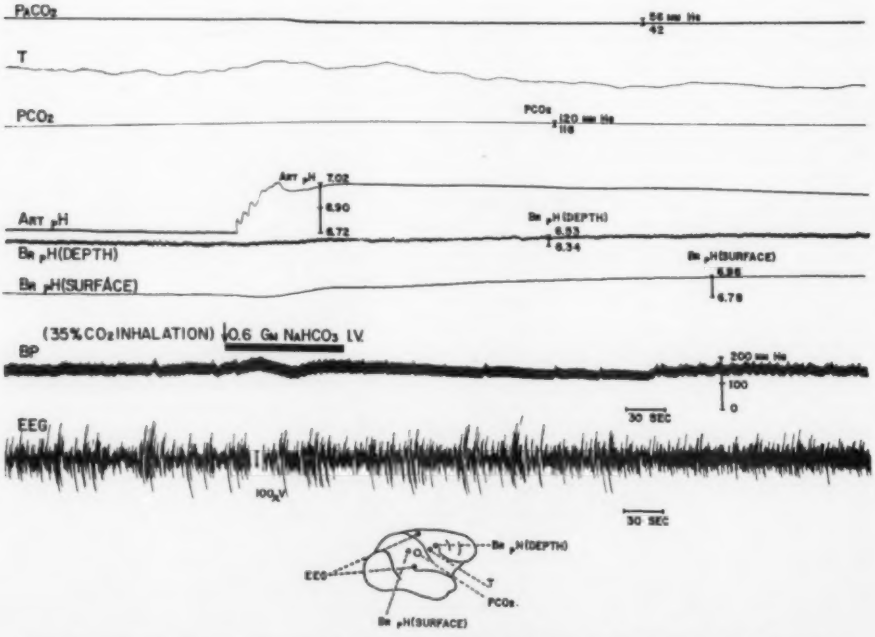

Fig. 7. Monkey. EEG improvement after intravenous injection of 0.6 gm. of sodium bicarbonate during continuous inhalation of mixture of 35% CO_2 and oxygen mixed with inspired air at constant rate of flow. After injection of sodium bicarbonate, arterial *p*H rose from 6.72 to 7.02 and brain *p*H at both depth and pial surface increased. Brain pCO_2 increased despite improved EEG. There was no remarkable alteration in blood pressure; T increased during injection and $PACO_2$ slightly at beginning of injection.

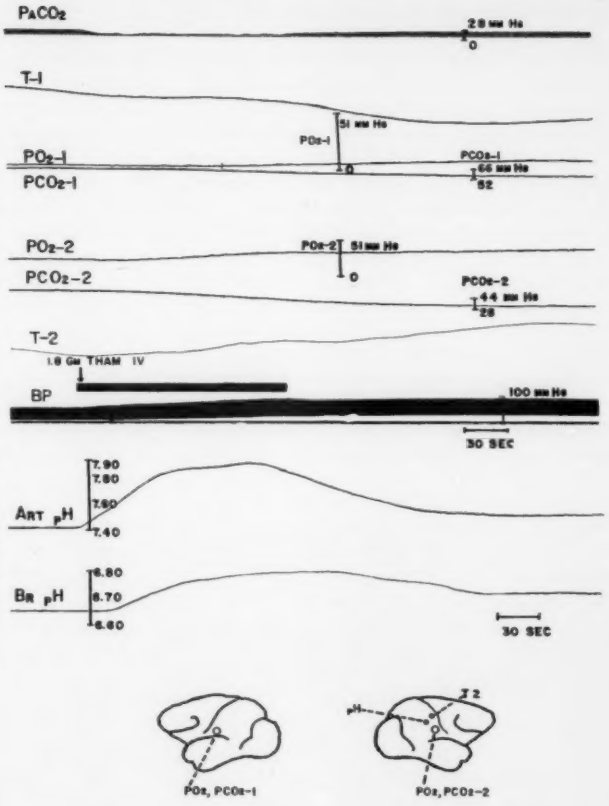

Fig. 8. Beneficial effects following intravenous injection of 1.8 gm. of THAM in monkey recovering from brain acidosis resulting from previous prolonged inhalation of 35% CO_2 and oxygen. Mixture had been discontinued before record, and 100% oxygen was inhaled at constant rate. Left carotid artery had been ligated at beginning of experiment. After intravenous injection of THAM, $PACO_2$ decreased and blood pressure increased. Arterial *p*H rose from 7.4 to 7.86 units and brain *p*H became more alkaline after delay (EEG record showed some improvement at this point but is not illustrated). Brain pCO_2 decreased. Cortical blood flow and oxygen tension increased in right hemisphere with intact circulation, but ischemic anoxia was present in left hemisphere due to ligation of carotid artery and fall in blood pressure resulting from cardiodepressor action of severe hypercarbia.

pO_2, *p*H, and pCO_2 levels, and unilateral electroencephalographic slowing was present before inhalation of the gas mixture. When CO_2 was inhaled, there was little further change in the ischemic hemisphere, but the usual electroencephalographic slowing appeared in the intact hemisphere as the brain pCO_2 and hydrogen ion concentration increased.

***p*H threshold for CO_2 narcosis at the depth.** Since lowering of brain tissue *p*H appeared to be the factor responsible for electroencephalographic slowing in CO_2 narcosis, it appeared likely that microglass *p*H electrodes thrust into the depths of the cortex would show changes comparable to those recorded from the pial surface. Possibly, at least part of the sensitive surface of these electrodes was located intracellularly. The microelectrodes were used concurrently with the larger surface electrodes in several experiments, and comparable changes were recorded at the depths except that the threshold was found to be 6.3 to 6.6 *p*H units. Possibly, the lower readings at the depths were due to traumatic interference with capillary circulation, or CO_2 and acid metabolites were less rapidly removed from within the tissues than at the pial surface, which has a richer circulation.

Effect of CO_2 narcosis during hypoglycemia. After hypoglycemia was induced in the fasting animal by insulin injection, the effect of CO_2 narcosis was studied in 2 experiments. Hypoglycemia itself causes electroencephalographic slowing and reduced brain pCO_2 and cortical blood flow (due to diminished metabolism and reduction of blood pressure). Since the elec-

troencephalogram is already abnormal, any threshold for further change due to CO_2 is difficult to define, but it was our impression that the threshold for CO_2 effect was lowered during hypoglycemia.

Acute asphyxia. It is possible that the effects of acute asphyxia on the central nervous system could be due to cerebral anoxemia or CO_2 narcosis. When asphyxia was induced in the curarized animal by discontinuing artificial respiration, brain pO_2 promptly fell to low levels and brain pCO_2 and hydrogen ion concentration gradually increased. Slowing of the electroencephalogram correlated best with the low levels of oxygen tension rather than the rise in brain pCO_2. With intermittent asphyxia, brain pCO_2 rose progressively; thus, the more chronic the depression of pulmonary exchange, the greater the tendency toward hypercarbia and central nervous system depression from this cause.

CO_2 narcosis due to obstruction of the superior vena cava. When the superior vena cava was clamped, capillary-venous outflow from the brain was obstructed and brain pCO_2 progressively increased. Usually, brain pO_2 also decreased, but, by incomplete or intermittent clamping, sufficient CO_2 retention within the brain could be induced to result in electroencephalographic slowing in the absence of cerebral anoxia.

Absence of demonstrable tissue buffering within the brain. Providing the threshold for tissue acidity was reached and the $PACO_2$ was maintained constant for several hours, electroencephalographic slowing persisted, brain pCO_2 levels remained constant, and there was no evidence of a shift of brain *p*H to the

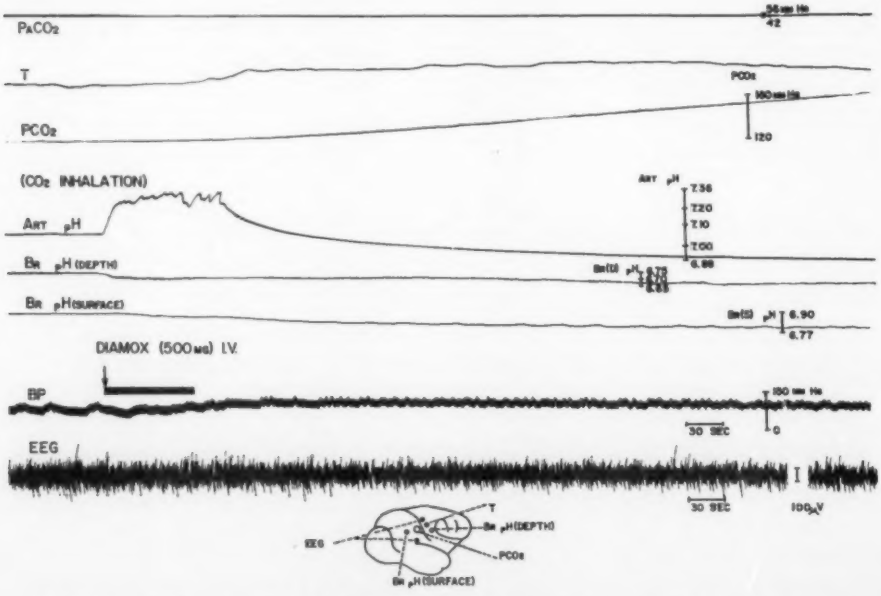

Fig. 9. Monkey. Deleterious effect of administration of Diamox (acetazoleamide) during impending CO_2 narcosis. Before intravenous injection of 500 mg. of Diamox, mixture of 35% CO_2 and 65% oxygen was gradually added to inspired air until brain *p*H at pial surface approached 6.9 units. Gas mixture was then maintained at constant rate of flow, and 500 mg. of Diamox was injected intravenously. In spite of temporary alkaline shift in arterial *p*H, since Diamox is alkaline preparation, brain pCO_2 rose and brain *p*H, at both depths and surface, fell. Some electroencephalographic slowing began after injection but is obscured by slow recording speed. Cortical blood flow and blood pressure increased.

alkaline side. There did not appear to be any intrinsic biochemical mechanism within the brain whereby buffering might occur and account for the adaptation that occurs in CO_2 narcosis. If CO_2 inhalation was discontinued and the $PACO_2$ was allowed to return to normal levels, electroencephalographic slowing disappeared as the *p*H of the brain rose. If once again CO_2 narcosis was induced, the electroencephalographic slowing appeared at a higher brain pCO_2 level, although the *p*H threshold remained the same. This data appeared to us to indicate that adaptation may occur due to increases in the buffer base of the blood, although changes in neuronal excitability may also play a part.

Effect of CO_2 narcosis on blood pressure. It was noticeable that, in high concentration, CO_2 tended to lower the blood pressure and slow the heart rate. One possible explanation for this observation is that CO_2 in high concentrations diffused through cardiac muscle fibers, lowered myocardial *p*H, and decreased the efficiency of myocardial contraction. In several experiments in which myocardial depression was present, the intravenous injection of sodium bicarbonate improved cardiac rhythm and increased the blood pressure.

Effect of oxygen breathing. Oxygen breathing increased PaO_2, SaO_2, and $PaCO_2$. The $PaCO_2$ increased because oxyhemoglobin associates less well with CO_2 than reduced hemoglobin.[20] The increase in $PaCO_2$ resulted in increased brain pCO_2 levels and further brain acidity.

DISCUSSION

Carbon dioxide in high concentration from exogenous or endogenous sources increases the pCO_2 of brain tissue. CO_2 diffuses rapidly across cell membranes and through tissues, forming H^+ and HCO_3^- ions. Usually, but not invariably, when brain pCO_2 levels exceed 75 to 100 mm. Hg, brain tissue *p*H (as measured at the pial surface) is lowered below 6.6 to 6.9 units and signs of depression of brain function appear, characterized by slowing of the electroencephalogram. A few bursts of spike activity may appear at this stage. Progressive reduction in brain *p*H eventually results in decreased amplitude of the electroencephalogram with a tendency toward flattening of the record. At this stage, there is a depressant action of CO_2 on spontaneous or induced epileptic spike activity. The *p*H threshold is the same for suppression of induced spike activity as for the production of slowing in a previously normal electroencephalogram. The view that tissue *p*H is a critical factor in depression of brain activity is supported by the intravenous injection of sodium bicarbonate, which tends to decrease the electroencephalographic abnormality as the brain *p*H increases despite the increases in arterial and brain pCO_2. Another observation supporting this view is that, in metabolic acidosis with low arterial and brain *p*H levels, inhalation of less CO_2 is required to lower the brain *p*H further and induce electroencephalographic change. Finally, when a state of localized brain acidosis is induced by vascular occlusion, the threshold for the electroencephalographic effect of CO_2 is lowered in the area of sluggish flow.

If the view that brain *p*H is a critical factor in producing CO_2 narcosis is correct, it may then be understood why arterial pCO_2 and *p*H levels often correlate poorly with cerebral symptoms, particularly since these experiments have clearly shown that brain pCO_2 and *p*H may differ widely from similar measurements of the arterial blood. The remarkable ability of CO_2 to penetrate living cells and cause intracellular acidity with more toxic effects than comparable changes in extracellular *p*H has been known since the experiments of Jacobs in 1920.[21] Such changes in cellular *p*H are accompanied by changes in ionic content of potassium and sodium, which are presently being investigated by us.

Therapeutic considerations. In CO_2 narcosis, therapeutic measures should be designed to restore brain *p*H to normal. This may be accomplished by removal of arterial CO_2 by improved pulmonary ventilation, by improving cerebral venous-capillary circulation, and by the intravenous infusion of alkaline substances such as sodium bicarbonate and THAM. Alkalinization by gastrodialysis[10] and administration of intravenous THAM in man[23] have both been shown to prevent or improve CO_2 narcosis. We believe the administration of acetazoleamide (Diamox) is dangerous since it tends to fix CO_2 in the tissues and decreases

brain *p*H further. The administration of CO_2 or acetazoleamide to human subjects with compensatory respiratory alkalosis in hepatic coma has already proved dangerous, presumably for similar reasons.[22]

Adaptation to CO_2 narcosis. The exact nature of adaptation to high levels of carbon dioxide remains undetermined, but no evidence was found in these experiments for any buffering effect at the tissue level. Adaptation may occur by increases of buffer base in the blood or possibly by changes in neuronal excitability. Our data, determined in vivo, tend to be in agreement with the measurements of Nichols[24] obtained from tissue slices removed from rats exposed to CO_2 for various intervals of time before sacrifice.

Several explanations for differences in individual susceptibility to CO_2 narcosis have been shown in these experiments. Any tendency toward metabolic acidosis or localized acidosis of brain tissue predisposes to the narcotic effects of CO_2. Conversely, any tendency toward metabolic alkalosis tends to protect against CO_2 narcosis. Cerebral ischemia and sluggish capillary-venous flow (which occur with such conditions as heart failure, increased venous pressure, and cerebral arteriosclerosis) predispose the individual to the narcotic effects of CO_2. If an area of brain has a localized area of sluggish blood flow, that area of brain will tend to show localized change.

The observation that breathing 100% oxygen tends to increase arterial and brain pCO_2 levels is of particular interest since the deleterious effects of oxygen breathing in CO_2 narcosis due to emphysema are well known.[3–5] Presumably, this mechanism plays a part in the disastrous effects of oxygen breathing as well as suppression of the anoxic drive to the respiratory center and the vasoconstrictive effect of oxygen on cerebral vessels.

In summary, our data support the view that CO_2 narcosis is not necessarily due to changes in molecular CO_2 of the blood nor to the concomitant arterial acidosis but rather to a specific property of CO_2 on neuronal function, namely, rapid intracellular diffusion with the rapid production of intracellular acidosis. While CO_2 retention in the brain is affected first and foremost by changes in arterial pCO_2, other factors such as the arterial *p*H, the metabolic state of brain tissue, cerebral capillary-venous flow, and the CO_2-carrying capacity of the blood must also be considered.

CONCLUSIONS

1. Excess CO_2 within brain tissue may be due to inhalation of exogenous gases having a high content of CO_2 or to retention of endogenous CO_2. Endogenous CO_2 retention within brain tissue may result from [1] diminished pulmonary ventilation, circulation, and other conditions associated with increased $PaCO_2$; [2] decreased cerebral capillary flow; or [3] diminished CO_2 transport by the blood which results from large doses of acetazoleamide.

2. CO_2 retained within brain tissue diffuses rapidly across cell membranes and lowers intracellular *p*H by combining with H_2O to form H^+ and HCO_3^- ions. Acidosis of brain tissue from other causes predisposes the brain to the narcotic effect of CO_2. Changes in the electroencephalogram correlate with the *p*H level of brain tissue and may occur in the absence of hypoxia. If the *p*H of the pial surface of the monkey cortex is reduced below 6.6 to 6.9 units, electroencephalographic abnormality regularly results. Electroencephalographic changes correlated poorly with brain pCO_2, $PaCO_2$, and a*p*H levels.

3. Ischemia of the brain predisposes it to CO_2 narcosis because acid metabolites are poorly removed by a sluggish circulation and brain acidity develops more rapidly than in brain tissue having intact circulation.

4. Epileptic spike activity present in the electroencephalogram before CO_2 inhalation tends to be reduced or abolished as the *p*H of the pial surface is lowered below 6.6 to 6.9 units.

5. The intravenous administration of acetazoleamide (Diamox) during CO_2 narcosis is potentially dangerous.

6. The intravenous administration of sodium bicarbonate during CO_2 narcosis increases blood and brain *p*H, in spite of an accompanying rise in arterial and brain pCO_2. Electroencephalographic abnormality present may show transient improvement during the alkaline shift of brain *p*H.

7. When arterial pCO_2 is held constant at high levels for several hours, brain pCO_2 and

*p*H and the electroencephalogram do not alter significantly. Adaptation to CO_2 narcosis may be mediated by increases in the buffer base of the blood or changes in neuronal excitability.

8. Possible explanations for individual differences in susceptibility to CO_2 narcosis include preexisting acidity of blood or brain, decreases in capillary-venous flow within the brain, and decreased CO_2-carrying capacity of the blood.

9. Oxygen administration during CO_2 narcosis is dangerous because it further increases arterial and brain pCO_2 levels, tends to further lower brain *p*H, causes cerebral vasoconstriction, and tends to inhibit the anoxic drive to the respiratory center.

THAM was supplied by Abbott Laboratories, North Chicago, Ill.

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Exacerbations in parkinsonism

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IN THE VAST LITERATURE dealing directly or indirectly with the medical treatment of parkinsonism, little attention has been paid to the occurrence of exacerbations, spontaneous or induced. The course of parkinsonism has been described as "always very chronic,"[1] "slowly progressive,"[2] and "gradual and relentlessly progressive,"[3] but it is pointed out that "30% of post-encephalitic cases seem to be static"[2] and that "encephalitic cases . . . may set in fairly acutely and become stationary after a time."[3] The general impression is of an almost inexorable downhill progression in which the plateaus, the "static periods," are widely described but the exacerbations have received scant attention and then mainly from Cooper[4,5] and Schwab.[6–8]

During the personal study of 109 patients with parkinsonism, I have been impressed by the frequency of exacerbations. These exacerbations fall quite readily into 3 groups: those precipitated by withdrawal of the patient's drug; those occurring in relation to various forms of stress or developing apparently spontaneously; and those induced by the ingestion of alcohol or other drugs.

DRUG WITHDRAWAL

Many drugs are available for use in the treatment of parkinsonism, but there is little agreement on a drug of choice. Schwab[9] pointed out that "there is no drug of choice" and no available preparation that has the "efficiency of insulin in diabetes." The analogy between drug treatment in parkinsonism and diabetes can be carried a stage further. The effects of withdrawal of insulin in a diabetic person are common knowledge, but withdrawal effects of antiparkinsonism drugs are less well-known. Critchley[10] mentioned incidentally that "as might be expected, cessation of drug treatment is followed by a relapse or exacerbation." He did not enlarge upon this point.

England and Schwab[6] stated that stopping antiparkinsonism drugs should not be undertaken lightly. They found that some patients were unaffected whereas others noticed "rapid increase in their symptoms particularly tremor, a marked slowing in motor activity and a disturbing sensation of fatigue, discomfort and anxiety." Some authors[2,11] discussed the confusional states that sometimes develop during antiparkinsonism drug therapy and advocated withdrawal to eliminate these toxic psychoses. Doshay[11] did not mention the dangers involved, but Porteous and Ross[2] drew attention to increase in tremors and rigidity in such patients.

The table lists 20 patients in whom antiparkinsonism drugs were withdrawn. It also records their age, duration of parkinsonism, and particulars of drug therapy. Scored functional ability while on drugs and later off drugs and the reason for drug withdrawal are indicated. The method of grading the functional ability is based on a scoring system for 5 representative functions: walking, mobility in bed, feeding, dressing, and morale. A score of 3 points for each function indicated normality, a score of 2 points partial disability, and 1 point severe disability, while 0 signified inability to walk, move in bed, feed, or dress or mental dependence. A total score of 14 or 15 out of the possible 15 was taken as normal; the classification for other scores is given in the footnote to the table.

Examination of the circumstances under which drugs were withdrawn is instructive. In 11, drugs were deliberately stopped to provide a base line before chemothalamectomy and in 3 before a change in drug therapy. Drugs were stopped in 2 patients during hospitalization, 1 after hematemesis and the other

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for stabilization of diabetes mellitus. In 1 patient, drug therapy was withdrawn by her private doctor, 1 ran out of tablets, and the remaining 2 stopped of their own volition. The temptation to obtain a scientific base line should be resisted in the interests of the patient. On admission to hospital, attention is customarily paid to a diabetic patient who states his daily insulin requirement, to a cardiac patient taking digitalis, or to an epileptic patient on anticonvulsants because the dangers of drug withdrawal are well recognized in these conditions. Similar concern for patients on antiparkinsonism drugs has been lacking. A patient with parkinsonism should be in a position to state the specific drug and the amount being taken and should be warned of the hazards of stopping or running out of medication.

The severity of symptoms which developed after drug withdrawal was not proportional to the length of time patients had received drugs or to the duration or severity of the illness. This point can be illustrated by the following case reports:

Case 12. A man aged 42 had experienced tremor of the left arm for two years. During this time, he had received benzhexol hydrochloride (Artane, trihexyphenidyl), 15 mg. daily, with improvement in the tremor and was little incapacitated by the disease. He neglected to visit his general practitioner to replenish his supply of tablets and, after three days without medication, suddenly collapsed and began "shaking all over." His doctor visited him and restarted his drugs. Although the "shaking" lasted only a few hours, he experienced general weakness which necessitated his remaining in bed for a week. The day after his sudden collapse, he complained of neuralgia-like pain in the muscles of the left shoulder girdle which persisted for two weeks. When he became ambulant once more, he found that his condition had deteriorated in that he now dragged the left leg.

Case 18. A man aged 45 had suffered from parkinsonism for twenty years and was considerably disabled. The main features of the disease in his case were quite severe rigidity in the right arm and leg, moderate rigidity in the left arm and leg, and minimal tremor of all limbs. He had taken 8 mg. of benzhexol hydrochloride daily for four years and was admitted to hospital for chemothalamectomy. In order to obtain a preoperative base line, his drug was stopped. After forty-eight hours, gross tremor appeared in all limbs and he was unable to feed himself or walk about. Forty-eight

EFFECTS OF DRUG WITHDRAWAL

Case no.	*Sex*	*Age*	*Duration in years of parkinsonism*	*of drug therapy*	*Drug administered (mg. per day)*	*Scored ability* On drug*	*Off drug*	*Cause of drug withdrawal*
1	M	52	11	10	Artane 6 mg.	11	8	Patient stopped
2	F	52	9	7	Artane 8 mg.	9	2	Prethalamectomy
3	F	65	8	3	Cogentin 6 mg.	9	7	Before new drug
4	M	59	4	½	Artane 10 mg.	13	10	Before new drug
5	F	57	20	11	Artane 10 mg.	3	1	Prethalamectomy
6	M	60	11	10	Artane 15 mg.	6	4	Prethalamectomy
7	M	54	9	9	Artane 6 mg.	5	4	Prethalamectomy
8	F	39	19	5	Lysivane 100 mg.	6	4	Prethalamectomy
9	F	51	6	2	Artane 6 mg.	12	8	Before new drug
10	M	41	8	5	Artane 15 mg.	9	9	Prethalamectomy
11	F	44	5	5	Artane 15 mg.	9	4	Withdrawn by private doctor
12	M	42	2	2	Artane 15 mg.	14	4	Ran out of tablets
13	F	52	5	2	Lysivane 100 mg.	5	4	Prethalamectomy
14	F	51	21	10	Artane 15 mg.	4	1	Prethalamectomy
15	F	54	34	8	Cogentin 6 mg.	7	4	Prethalamectomy
16	M	49	37	1	Artane 8 mg.	11	9	Prethalamectomy
17	M	69	5	4	Artane 6 mg.	2	1	Patient stopped
18	M	45	20	4	Artane 8 mg.	6	1	Prethalamectomy
19	F	67	6	6	Artane 15 mg.	9	4	Stopped in hospital after hematemesis
20	F	63	6	2	Cogentin 10 mg.	9	5	Stopped in hospital during stabilization of diabetes mellitus

*A score of 14-15 = normal; 11-13 = slightly handicapped; 8-10 = moderately handicapped; 5-7 =considerably handicapped; 2-4 = severely handicapped; 0-1 = totally dependent.

hours later, he was almost completely paralyzed by gross rigidity and was unable to raise the arms or bend the elbows beyond 30°. His medication had to be reintroduced.

Case 5. A woman aged 57, severely incapacitated by parkinsonism of twenty years' standing, was admitted to hospital for chemothalamectomy. She had severe rigidity of all limbs, left more than right, and minimal tremor of the right arm. She had received 10 mg. of benzhexol hydrochloride daily for ten years. Two days after this drug was stopped, she experienced somnolence and a feeling of indescribable weakness. She complained of heaviness of the eyelids and difficulty in keeping them open. Her voice, which had been quiet and hesitant, became inaudible, and it was almost impossible for her to open her mouth. She drooled saliva and experienced excessive sweating and fecal impaction developed. There was no increase in tremor, but rigidity was gross. It proved necessary to restart drug therapy.

It is noteworthy that, among the 20 patients, there was an element of bradykinesia in 18 while on medication. The most common feature which developed after drug withdrawal, occurring in all patients except 1 (Case 10), was a feeling of increased weakness and uselessness. The comments of some of the patients are of considerable interest: "My limbs are useless" (Case 9); "so weak I couldn't lift a duster" (Case 11); "descended to the level of something that crawls" (Case 13); "I feel like a statue—in a state of suspended animation" (Case 7).

Of the 20 patients listed in the table, 9 had unilateral tremor. In 4 of these (Cases 3, 12, 15, 19), tremor became bilateral and worsened on the affected side in 2 (Cases 9, 16); 3 were unchanged (Cases 2, 5, 13). Bilateral tremor was already present in 11 patients and, of these, 6 worsened (Cases 1, 4, 6, 11, 18, 20) and 5 showed no change (Cases 7, 8, 10, 14, 17). There was no change in degree in 5 of 8 patients with minimal tremor (Cases 5, 7, 8, 14, 17), while tremor became worse in 3 (Cases 1, 6, 18) and gross in Case 18.

Rigidity was present to a varying degree in all 20 patients. It was bilateral in 16 and unilateral in 4 (Cases 9, 12, 13, 16). Drug withdrawal had no effect in 3 of the 4 unilateral cases, but rigidity was increased on the affected side in Case 16. There was no change in 6 bilateral cases (Cases 3, 7, 8, 10, 11, 15), whereas in the remaining 10 (Cases 1, 2, 4, 5, 6, 14, 17, 18, 19, 20) rigidity was worsened after drug withdrawal. There was no change in tremor or rigidity in 3 patients (Cases 7, 8, 10) when their drugs were stopped.

Muscular pain had been a troublesome intermittent symptom in 10 of the 20 patients before drug withdrawal. When drugs were stopped, 6 patients complained of severe muscle pain which was nuchal in 4 (Cases 1, 3, 4, 17), in the left forearm in Case 12, and in the right hip in Case 19. Cases 12 and 17 had never experienced muscle pain before. Pain has been an infrequently reported feature of parkinsonism, although 1 of the patients described by James Parkinson[12] was said to have been violently affected with rheumatic pain to the finger ends. Rheumatoid pain was mentioned by Oppenheim[1] as an early symptom but one which was seldom marked throughout the course of the disease. Walshe[13] stated that "Aching pain in the shoulder and arms may be complained of, and also painful flexion cramps in the toes." In a study of 109 patients with parkinsonism, 15 presented and 56 later had muscle pain.[14]

Before drug withdrawal, speech was affected in 17 of 20 patients. This speech disturbance consisted of monotony and quietness of voice in 8 (Cases 2, 3, 7, 8, 10, 11, 13, 19), monotony, quietness, and hesitancy in 5 (Cases 1, 4, 5, 17, 20), palilalia in 2 (Cases 6, 14), and indistinctness in 2 (Cases 15, 16). When medication was stopped, there was general worsening of speech in all except 2 patients (Cases 4, 11), while 5 became unintelligible (Cases 6, 7, 14, 15, 17). Speech became more quiet in 3 (Cases 9, 12, 18) where it had previously been normal on drugs.

Increased salivation was present in 12 patients. After drug withdrawal, it became more troublesome in 11 of the 12 and developed in 6 more (Cases 1, 3, 9, 12, 19, 20). Cases 11 and 13 did not have salivary increase. Nasal secretions became profuse in 3 patients (Cases 7, 14, 17) after removal of drugs. Nausea and vomiting developed in 2 patients (Cases 1, 3) forty-eight hours after drug withdrawal.

England and Schwab[6] stated that some patients were unaffected after drug withdrawal. In my series of 20 patients, only Case 10 was relatively unaffected when his medication was eliminated; however, speech became quieter and salivation more troublesome in that pa-

tient. Considerable experience with various types of parkinsonian patients undergoing surgery on the basal ganglia has enabled England, Schwab, and Peterson[15] to predict which patients will react unfavorably. They have observed that electroencephalographic changes and akinesia were indications that a patient would not benefit greatly by neurolytic surgery and that such surgery was actually hazardous. Transient marked exaggeration of parkinsonian symptoms was noted by Cooper[4] in some patients after chemopallidectomy or thalamectomy. He called this "hyper-parkinsonism crisis" and found that such a crisis was more likely to develop in advanced cases with mental deterioration. There are no similar indexes to predict whether a patient with parkinsonism will react untowardly when drugs are withdrawn. It is suggestive that akinesia was a prominent feature in 18 of the 20 patients in my series and electroencephalographic abnormalities existed in 13.[14] Mental deterioration existed only in Case 17. Obviously, the series is too small to draw any conclusions.

Although Schwab and England[16] encountered improvement in untreated patients when a proper combination of drugs was instituted, this improvement was rarely more than 25% in the majority of cases. Boshes[17] stated "we see a wonderful response for a short while, then an adaptation of the body to the medication so that it is no longer so effective." It might be argued that the effects of drug withdrawal are simply the result of unmasking the natural disease. This may be true, but it seems possible that sudden drug withdrawal can produce a hyperparkinsonism crisis, just as withdrawal of anticonvulsants can precipitate status epilepticus in a hitherto well controlled epileptic patient. The remarkable consistency with which exacerbations occurred forty-eight to seventy-two hours after drug cessation would seem to preclude the possibility that the stress of hospitalization or apprehension before operation could be responsible.

In this discussion on the effects of drug withdrawal, there remain several unusual features which either developed or were made worse by stopping antiparkinsonism drugs.

Oculogyric crises are a well recognized but nowadays relatively rare feature of parkinsonism (estimated at 4% by Garland[18]) and are thought to be diagnostic of a previous encephalitis. Less recognized, yet more frequently occurring, are episodes in which there is drooping of one or both eyelids, incidents in which there is a temporary inability to raise the eyelids, and attacks in which the eyelids remain closed for prolonged periods despite efforts on the patient's part to open them. Unlike oculogyric crises, these eyelid dysfunctions seem to occur in paralysis agitans as well as postencephalitic parkinsonism. Marinesco[19] described several patients with encephalitis lethargica who had difficulty opening the eyes and spent most of the day with their eyes closed, yet were apparently awake. Three months after encephalitis, parkinsonism developed in 1 of these patients, a boy of 21, and at that stage he still had difficulty opening the eyes. "Attacks of closed lids" were described by Hall in encephalitis lethargica[20] and as a sequel to that disease.[21] He regarded the phenomenon as a variation of oculogyric crisis but pointed out[20] that "there is no sign of any spasm of the orbicularis oculorum." He also wrote[21] that in oculogyric crises "the actors hurry off the stage before the curtain falls" and in eye-closure attacks "the curtain cannot be rung up because the actors will not take up their proper positions on the stage. In either case it is very disturbing to the management!" Schwab[22] regarded difficulty in opening the eyes as being more rare than oculogyric crises.

In a personal study of 109 patients with parkinsonism, 17 experienced eyelid dysfunction, whereas only 8 suffered from oculogyric crises. It is instructive to observe the effect of drug withdrawal on these symptoms.

Among the 20 patients listed in the table, oculogyric crises occurred in 1 (Case 15) and there were 8 in whom eyelid dysfunction was a feature before drug withdrawal; 3 of these patients complained of drooping eyelids. This feature was unilateral in 2 (Cases 4, 9), and it is noteworthy that the lid involved was on the more severely affected side. Although the third patient (Case 19) experienced bilateral eyelid drooping, this was more pronounced on the side predominantly affected by parkinsonism. Temporary inability to open the eyelids occurring in the other 5 patients was unilateral in 2 (Cases 7, 16) and bilateral in

3 (Cases 6, 14, 17). When drugs were stopped, there was no change in 1 (Case 4), general worsening occurred in 4 (Cases 7, 9, 16, 19), and 3 (Cases 6, 14, 17) experienced attacks in which they were unable to open the eyes for hours at a time although there was no sign of spasm of the ocular muscles. Cases 14 and 17 gave the appearance of being asleep all day but were apparently aware of their surroundings. A further patient (Case 5) had temporary inability to open the eyes and a retroorbital aching sensation. Oculogyric crises occurred with such frequency in Case 15 that the term status oculogyrus seemed appropriate.

It would appear that, if eyelid dysfunction or oculogyric crises occurred in a patient with parkinsonism, these symptoms became more troublesome following drug withdrawal.

Nystagmus is not a feature of uncomplicated paralysis agitans but is sometimes seen in postencephalitic parkinsonism,[23] and "nystagmiform movements" were seen in encephalitis lethargica.[20] Case 8, a patient with postencephalitic parkinsonism, showed nystagmus while on medication; 2 patients (Cases 2, 7) who had no history of past encephalitis had nystagmus when drugs were withdrawn, and the sign became more marked in Case 8.

Cases 14 and 17 had catatonia of the arms after drug withdrawal:

Case 14. A woman aged 51 first had symptoms of parkinsonism twenty-one years earlier and was now disabled by severe rigidity affecting all 4 limbs. Tremor was not a feature. She had taken 15 mg. of benzhexol hydrochloride daily for ten years. For eleven years, she had been bathed, dressed, and turned in bed but was still able to feed herself with a spoon and walk slowly with support, although walking backward was easier for her. Her voice was quiet, and palilalia was a feature. She had no psychotic symptoms, and her family was not aware of any mental failure, but she was overdemanding. Salivation had been excessive for eleven years. She was admitted to hospital for chemothalamectomy. Drugs were stopped, and, after forty-eight hours, she was completely helpless, being unable to feed herself or walk. Speech became inaudible and unintelligible, but I noticed that in her sleep she occasionally shouted out in a loud voice, apparently during nightmares. She was unable to open the mouth on command, although she seemed to have little difficulty doing so when being fed. There was inability to open the eyes. She drooled saliva almost continuously, and nasal secretions were excessive. She had no hyperpyrexia or vomiting. Rigidity was gross in all limbs, and there was catatonia of the arms which, when placed in any position, remained there until moved. She had no pyramidal tract signs, and neither psychotic symptoms nor incontinence developed. Chemothalamectomy was performed with no appreciable improvement, and the patient was discharged home. Despite the recommencement of medication, her "state of suspension" persisted; she was admitted to a local hospital and died two weeks postoperatively. No postmortem examination was performed.

Case 17. A man of 69 had suffered from parkinsonism for five years and had received 6 mg. of benzhexol hydrochloride daily for four years. The main feature of the disease was quite severe rigidity of all 4 limbs. Tremor was negligible. For one year, he had experienced episodes of confusion during which he became hallucinated and his speech rambling in character. In more recent months, there had been further deterioration with urinary and fecal incontinence and increased somnolence. He exhibited many compulsive phenomena such as moving chairs, piling up cushions, putting ornaments into drawers, hiding his handkerchief and then searching for it, and sitting tearing up paper and dropping it about. He was seen in November 1959 and on examination exhibited quite severe rigidity of the limbs, with a slow gait and scuffing of the right leg. Conversation was impossible, but he uttered a few relevant phrases occasionally in a quiet, indistinct voice. He continued with little change until March 1960, when he neglected to take his tablets. On the third day off medication, while out walking he suddenly collapsed and was admitted to hospital as an emergency medical problem. He was found to be irrational and confused. Apart from scattered rhonchi in the chest, there were no physical signs ascribable to any condition other than parkinsonism. He was unable to open the eyes or to open the mouth or protrude the tongue on request, although the nurses had no difficulty in feeding him. His voice was quiet and almost unintelligible, but sometimes he would shout out coherently, in a loud voice, about not wanting to live to be a nuisance to his relatives. There was severe rigidity of the limbs and general helplessness. He exhibited catatonia of the arms and bilateral grasp reflexes but no pyramidal tract signs. He had increased salivation and nasal secretion as well as occasional urinary and fecal incontinence. He was transferred to a hospital for chronic sick and died shortly afterwards.

Brain[24] stated that in arteriosclerotic parkinsonism "catatonia is not uncommon." Similarly, Critchley[25] claimed that catatonia was one of the most characteristic features of arteriosclerotic parkinsonism, particularly in patients with pseudobulbar signs or dementia and incontinence. He was of the opinion that true catatonia is rarely seen in paralysis agitans.

If arteriosclerotic parkinsonism exists as an entity, Case 14, with symptoms dating from the age of 30 years, certainly does not fall into this category. She did not exhibit dementia, incontinence, or pseudobulbar signs. Her speech was quiet with palilalia, becoming unintelligible after drug withdrawal, but, as Fairman and Cooper[26] pointed out, dysphonia may merely reflect stiffness and weakness of the vocal cords. Indeed, it is interesting that her voice was quite strong during sleep. The clinical findings in Case 17 approximate more closely to those described by Critchley[25] in patients with arteriosclerotic parkinsonism who showed catatonia. However, catatonia did not develop in either Case 14 or 17 until drugs were withdrawn. Case 17 also then had grasp reflexes, and this feature has been described in arteriosclerotic parkinsonism by Critchley.[25]

SPONTANEOUS OR STRESS-INDUCED EXACERBATIONS

In a study of 109 patients with parkinsonism, 15 exacerbations developed in 13 patients, occurring over a range of six months to nineteen years after the onset of the disease. Schwab and Prichard[7] reported that "some investigators believe that a sudden change in the severity of the disease is always due to an external cause." There was no obvious cause for 7 of the 15 exacerbations in my series, and the following 2 case reports are typical.

A.G., a man of 51, had suffered from parkinsonism for five years and had received 15 mg. of benzhexol hydrochloride daily for four years. The main features of the disease were moderate rigidity of all 4 limbs, left more than right, together with moderate tremor of the arms. He was moderately handicapped. One day, while preparing to go out for a walk, he suddenly collapsed. He complained of cramp-like pain in the back of his neck and head and in the left upper arm. His whole body was shaking, and he could not use his limbs. He was carried to bed and undressed by his wife. In the following weeks, although his medication was continued, he had to be washed, dressed, fed, and turned in bed. During this time, his speech was thick and quiet, he had some difficulty in swallowing, and salivation was excessive. He was in bed for two months, and, when he was at last able to get up, there was marked retropulsion of gait. As his speech returned, it was gabbling and exhibited features of propulsivity. After this exacerbation, he gradually improved, but his gait was shuffling and he was generally worsened.

G.H., a woman of 39, had complained of dragging the right leg and cramps in both feet for three months, but she was not receiving any medication. She awakened one morning and dressed feeling perfectly well. Then, without warning, she fainted. When she regained consciousness, her head and all 4 limbs were shaking violently, which state persisted for several days. Her doctor visited her and prescribed barbiturates, which had no beneficial effect on her condition. The administration of benzhexol hydrochloride gradually relieved the shaking, but tremor of the arms persisted. The patient's condition was generally worsened as a result of the exacerbation.

Of the exacerbations, 8 appeared to have been related closely to varied forms of stress: physiologic, 1 case; infective, 3 cases; traumatic, 1 case; and emotional, 3 cases. The following case reports are representative:

G.P., a 36-year-old woman, had experienced heaviness of the right leg with a tendency to scuff the right foot for three years. She was not receiving any medication. She became pregnant, and, during the second trimester, tremor of the right hand developed and persisted until delivery. The tremor then disappeared and did not reappear until four years later.

V.R., a woman of 52, had complained of static tremor of the right hand for two years. The tremor did not incapacitate her. She had been unable to tolerate any medication. During a severe attack of influenza, the tremor spread to involve the whole of the right arm. However, as she recovered from the infection, the tremor gradually subsided and returned to its previous level.

D.J., a 49-year-old man, first had symptoms of parkinsonism nine years previously and had moderate rigidity of the left arm and leg and moderate tremor of the left arm. One day, he was caught between 2 oil drums at the colliery where he was employed but sustained no serious injury. However, because he was "shaking all over," he was taken to hospital where he was detained for four days and was unable to work for four months. Since this exacerbation, the left leg has been tremulous and his gait much slower.

V.P., a man of 42, was moderately disabled by rigidity and tremor of the left arm and leg and had been receiving benzhexol hydrochloride, 20 mg. daily, for five years. While being driven in a car, he witnessed an accident in which his nephew was killed. His arms began to shake so violently that his fingers were not visible. This attack subsided after three or four hours, but his condition progressed more rapidly thereafter.

Although Cooper[3] observed that severe reactions to stress were more usual in "the rapidly progressive malignant form of the dis-

ease," I could not confirm this observation. As has been mentioned previously, exacerbations occurred over a range of six months to nineteen years after the onset of parkinsonism, and the duration to date of the disease varied from one to twenty-seven years. Schwab and Prichard[7] found that an emotional upset might produce "permanent changes for the worse" in some parkinsonian patients. Cooper[5] stated that, during the course of parkinsonism, a stressful situation such as operation or psychologic or physical trauma "is often followed by marked exacerbation of all parkinsonian symptoms which may last for months or which may accelerate the progress of the disease." In 11 of the 13 patients, there was a general worsening of the condition after an exacerbation. Cases G.P. and V.R. returned to their preexacerbation level.

EFFECT OF ALCOHOL AND OTHER DRUGS

Schwab[22] recommended careful supervision of patients "accustomed to taking one or two drinks of whisky per day" while adjusting drug therapy, for it was difficult to distinguish overdrinking from hypersensitivity to the pharmacologic agents. On the other hand, Schwab and England[27] mentioned that some of their patients found "that a glass of beer or a whiskey and soda before they go to bed helps their sleep."

In my series of 109 parkinsonian patients, there were 56 nondrinkers while the remaining 53 were occasional to moderate drinkers. Among these 53 were 30 in whom alcohol appeared to have no effect on their parkinsonism; 6 noticed some albeit transient improvement, while in 17 there was temporary but definite worsening of their condition. Although 6 claimed some amelioration and indeed 1 experienced "more help from alcohol than from Artane," not one took alcohol frequently, for all 6 were definitely worse on the day after alcohol ingestion.

As might be expected, the 17 patients who found that alcohol worsened their state could rarely be persuaded to drink alcohol. It was generally agreed by them that even 1 glass of ale would cause marked weakness, increased tremor, and speech difficulty. A man whose symptoms were worsened by alcohol gave a history going back many years before the diagnosis of parkinsonism of definite neck stiffness and speech slurring after a single glass of beer—he had called the sensation "Bass head."

There are conflicting views on the response to general surgery of patients with parkinsonism. Cooper[28] stated that these patients tolerate anesthesia poorly, and England and Schwab[29] found an unfavorable reaction to the stresses of general surgery. Doshay,[11] discussing fractures as one of the problem situations occurring in the course of parkinsonism, wrote "even the oldest and the most fragile-looking patients with paralysis agitans tolerate these operations surprisingly well."

In my series of 109 patients, a total of 14 operations under general anesthesia had been performed for general disorders in 13 patients. None were observed during these operations, but, on the evidence of patients and relatives, it would appear that in 6 patients (7 operations) there was considerable and persistent deterioration dating from the operative procedure. In 7 patients (7 operations), no change in the parkinsonian state was noted after operation. It must be mentioned here that 4 of the 6 patients (5 operations) who showed worsening were siblings.

Of all complications which may follow surgery under general anesthesia, pneumonia is one of the most common. The majority of patients with advanced parkinsonism have lung complications from dysphagia and a rigid chest wall.[30] They are therefore more prone to pneumonia postoperatively. Nugent and associates[31] performed respiratory studies on 9 patients with parkinsonism, 5 of whom complained of dyspnea on mild exertion and in whom there was no cardiac or obvious respiratory disease. In these 5 dyspneic patients, the maximum breathing capacity was only 56% of normal. While receiving drugs, 2 patients had greater maximal breathing capacities than they had before treatment. It would seem logical to suppose that maintaining patients on antiparkinsonism drugs before and after operation might protect them from chest infection by maintaining their respiratory function at a more normal level.

Adverse side effects of other drugs have been recorded when used in cases of parkinsonism. Schwab and England[27] reported that

some patients reacted "very poorly to barbiturates such as pentobarbital and are restless in spite of it." These authors recommended the avoidance of chlorpromazine, prochlorperazine, and reserpine, which are known to induce a parkinsonism-like syndrome and have a deleterious effect in a patient already suffering from parkinsonism. Oppenheim[1] wrote, "I have done harm in one case by prescribing a preparation of salicylate and in another Dover's powder. Hyper-hidrosis which persisted and was very troublesome, commenced from that time." Oppenheim saw tremor and lateropulsion develop in a gouty patient due to colchicum poisoning. These symptoms reminded him so much of paralysis agitans that he was about to make the diagnosis, when the symptoms disappeared as the dose of colchicum was reduced.

I have had no experience of the harmful effects of the drugs mentioned by the above authors.

SUMMARY

Parkinsonism is usually described as a chronic progressive disorder in which static periods may occur. I have drawn attention to the little-recognized fact that exacerbations are not uncommon and may adversely influence the progression of the disease.

The varied situations in which antiparkinsonism drugs are withdrawn and the hazards of such elimination have been emphasized.

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Intermittent spinal ischemia

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THE TERM intermittent spinal claudication was used by Dejerine[1,2] to describe a syndrome consisting of transient weakness in the lower extremities with exertion in the presence of normal sensation and peripheral pulses. Eventually, there was progression to spasticity, sphincter incontinence, and loss of libido. These patients had positive serologies, and it was assumed that the spinal cord involvement was secondary to luetic arteritis of the lumbar segmental vessels. With the decline in the incidence of lues, clinicians have been more reluctant to attribute vascular insufficiency of the spinal cord to this disease. Embolic phenomena and atherosclerosis have been found to be more common etiologies. The diagnosis of vascular insufficiency as the etiology of myelopathy, especially in the lumbar cord, is often difficult to make. The patient may present with low back and hip pain, transient paresthesias, paresis, and sphincter incontinence. The symptomatology may progress and become permanent while a fruitless search for a spinal cord or vertebral etiology such as "myelitis" or herniated nucleus pulposus is made. A case of vascular insufficiency of the spinal cord will be presented with a review of the literature in an attempt to indicate the important neurologic symptoms and signs and their relative frequency.

CASE PRESENTATION

D. W. H., a 42-year-old white male janitor, was admitted to the Neurology Service of the Minneapolis Veterans Administration Hospital on June 24, 1960, complaining of "weakness in the lower extremities on exertion." His first admission to the Minneapolis Veterans Administration Hospital was on January 27, 1959, due to "back pain." At that time, he was a patient on the Orthopedic Service. His main complaint was pain in the lumbar region which did not radiate to the legs. The pain was aggravated when he lifted heavy objects and when his back was twisted suddenly but not when he coughed or sneezed. His left leg would tire when he walked. Examination revealed a full range of motion with some pain in the low back on extreme flexion and extension. There was tenderness to percussion over the L5 spinous process. No pain was present with straight leg raising. Muscle volume and strength were normal. Treatment consisted of bed rest with bedboards and later Williams exercises. Since Williams exercises aggravated his backache, they were discontinued and he was discharged.

At the time of his present admission, further questioning disclosed that he had had trouble with his left leg for the previous ten years. He had been a telephone lineman and noted tingling of his left thigh and hip when walking. He believed this was due to pressure from his safety belt or pants belt so he carried his safety belt and used suspenders; however, the tingling continued. Five years before admission, the patient fell from a telephone pole but did not suffer any serious injuries. As a precaution, his insurance company requested a thorough examination. He was told that roentgenograms of the pelvis revealed calcification in the pelvic vessels. As a result, abdominal aortography was performed and occlusion of the left common iliac artery was found. No definitive procedure was done, and the patient was discharged. In the succeeding five years, the patient noted an increase in paresthesias in the left leg with exertion. If the exertion continued, he often noted mild urinary incontinence and the passage of flatus; on at least one occasion, he soiled himself. In the past few years, he had noted in addition a decrease in his ability to maintain an erection.

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Physical examination revealed a well developed, well nourished 42-year-old male. Blood pressure was 129/88, pulse 88 (regular), and temperature normal. The general physical examination was normal. Examination of the peripheral pulses revealed that the pulsations were absent in the left femoral artery and decreased in the right. The left lower extremity was slightly cooler than the right, and the hair and nails were normal. Neurologic examination revealed normal cranial nerves. Sensation was normal. Muscle tone, volume, and strength were normal. Examination of the deep tendon reflexes revealed absent Achilles reflexes bilaterally. When asked to hop for ten minutes on his left leg, he stated that the leg was "numb and would soon collapse." However, examination failed to reveal any muscular weakness or sensory loss.

Laboratory examination revealed normal urine, hemogram, blood urea nitrogen, and fasting blood sugar, and the VDRL was nonreactive. Roentgenograms of the lumbar spine revealed minimal marginal sclerosis and mottling about the inferior portion of the right sacroiliac joint and minimal marginal hypertrophic lipping in the lumbar and lower thoracic spine, without appreciable joint space narrowing. Anteroposterior and lateral films of the abdomen revealed no calcification within the walls of the aorta.

Oscillometry revealed a 90% and 80% loss in circulation below the left and right upper thigh, respectively. A walking test revealed tiring in the left calf after 60 steps, tingling in the left toes at 120 steps, and cramping in the left calf at 150 steps.

Hospital course. With all the above history and findings, we felt that the patient now had proximal extension of the left iliac thrombus into the abdominal aorta. He was operated upon and found to have a complete occlusion of the terminal aorta ascending to 1½ in. below the renals and descending into both common iliac arteries. A Teflon graft was placed just above the occlusion and anastomosed in an end-to-side fashion with both external iliac arteries. Subsequent to this operation, the patient had good peripheral pulses and increased exercise tolerance and was able to maintain an erection.

DISCUSSION

It is beyond the scope of this paper to describe in detail the blood supply of the spinal cord. More thorough works on this subject are found in the papers of Kadyi[3] and Suh and Alexander.[4] Suffice it to say that the cord derives its blood supply from a pair of posterior spinal arteries and a single anterior spinal artery, which run its entire length. In turn, these vessels are fed from the radicular arteries of the vertebrals and aorta. There are only 6 to 8 anterior radicular arteries and 5 to 8 posterior radicular arteries; 3 to 5 anterior radicular arteries are found in the cervical region —2 in the thoracic and 1 to 3 in the lumbar area. The largest radicular artery exclusive of the vertebrals to reach the cord is the anterior radicular artery of the lumbar area, the arteria radicularis magna. This vessel occurs most frequently at the second lumbar segment but may be found anywhere between the eighth thoracic and fourth lumbar segments. Yoss[5] and Otomo, Van Buskirk, and Workman[6] have shown that the blood flow in the cervical region is in a caudal direction, while below this region the flow is cephalic. This implies that the blood supply to the thoracic, lumbar, and sacral regions of the cord is heavily dependent on the arteria radicularis magna of the lumbar area. Insufficiency in this vessel could easily lead to loss of function in the lower cord.

Cases of permanent spastic or flaccid paraplegia and sensory loss with or without sphincter impairment due to atherosclerosis, embolic phenomena, and dissecting aneurysm have been reported by Gull,[7] Bramwell,[8] Bristowe,[9] Hunt and Cornwall,[10] Hirsch,[11] Antoni and Lindgren,[12] Cook,[13] and Tuohy, Boman, and Berdez.[14] One of Cook's cases, with a sudden onset of sphincter incontinence and mild paraparesis, so resembled an intradural lesion that laminectomy was done before a vascular occlusion was thought of and demonstrated by aortography. In the cases of transient lumbosacral cord ischemia reported by Moxon,[15] Erb,[16] Dejerine,[1,2] Reichert, Rytand and Bruck,[17] Bergmark,[18] Goetz,[19] and Gilfillan and associates,[20] transient paresis and sensory changes were seen more frequently than sphincter incontinence.

One of the earliest descriptions of intermit-

tent claudication in the lower extremities was written by Charcot,[21] who noted cramping pain and absent peripheral pulsations in a patient who had an aneurysm in the right "primitive iliac artery" partially obliterating the vessel.

Dejerine separated intermittent spinal claudication from Charcot's intermittent claudication by these features: In intermittent spinal claudication, the arterial pulsations in the lower extremities are intact, pain and vasomotor disturbances are absent, and neurologic signs are present, that is, altered reflexes, impairment of sphincter control, and genital disturbances. Dejerine's criteria hold only for involvement of the lumbar segmental arteries and their peripheral branches, as is assumed in the cases reported by Moxon, Erb, Dejerine, and Bergmark. With insufficiency of the terminal aorta, absent or decreased peripheral pulses occur. The sensory changes occurring vary from numbness, tingling, and burning to severe pain in the low back, buttocks, hips, and thighs with exertion. The low back pain may lead to exploratory laminectomy as occurred in a patient reported by Gilfillan.

Gilfillan classified the types of claudication pain associated with various levels of vascular obstruction from the abdominal aorta down to the femoral-popliteal system. With terminal aortic obstruction, walking can produce severe pain first in the buttocks, then in the thighs and legs. With only obstruction of the parietal aortic branches, unilateral or bilateral lumbar and hip pain may develop with exertion. In total iliac obstruction, pain may begin in the buttocks with extension to thigh and calf on the affected side. This may resemble nerve root irritation and cause difficulty in diagnosis. Partial iliac obstruction may be associated with pain beginning in the calf and ascending to the thigh. Femoral profunda obstruction may cause pain in the anterior and medial aspects of the thigh. The well known claudication pain in the popliteal and calf region is seen with superficial femoral and femoral-popliteal occlusion.

Statistics regarding the incidence of thrombosis of the abdominal aorta or of spinal cord symptoms in thrombosis of the abdominal aorta are difficult to find. Kramer, Perilstein, and DeMedeiros[22] analyzed 3,000 consecutive cases of peripheral vascular disorders and found evidence of pathologic changes in the abdominal aorta in 207; 107 had radiologic evidence of calcification without impaired circulation, and 100 patients had subjective and objective evidence of occlusive disease. Among the 100, hip pain was seen in 16, paresthesias in 57, and impotence in 2. Evidence of complete aortic occlusion was noted in 36 of the 100; there was hip pain in 5 and paresthesia in 18, but none was impotent. Dragescu, Radu, and Petrescu[23] collected 37 cases of thrombosis of the abdominal aorta and found paraplegia in 7.

Lueth[24] reported 1 case of aortic thrombosis in 1,047 autopsies with no associated neurologic symptoms.

The case we have presented demonstrates intermittent spinal cord ischemia in a patient with terminal aortic thrombosis. Our case differs from those reported with permanent neurologic deficit secondary to aortic occlusion in that our patient had an adequate spinal circulation at rest. On the other hand, it differs from a typical Leriche syndrome[25,26] by the absence of global atrophy of the lower extremities, extreme fatigability of the lower extremities, and pallor of the lower extremities even when standing, which are manifestations of deficient peripheral circulation.

In our case, the thrombus extended far enough proximally to cause transient spinal ischemia with exertion and yet apparently developed slowly, so as to allow formation of an adequate collateral circulation preventing obvious peripheral ischemia.

SUMMARY

1. A case of intermittent spinal claudication secondary to low aortic obstruction is reported.

2. A brief review of the literature is presented.

3. A plea is made for recognition of the possibility of vascular obstruction in the abdominal aorta or lumbar segmental vessels in cases of transient or permanent spinal cord symptoms in the thoracolumbar sacral cord.

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Neurology

BOOK | REVIEWS

Injuries of the Brain and Spinal Cord and Their Coverings

edited by Samuel Brock, M.D., 739 pp., Springer Publishing Co., New York City, 1960. $18.50.

The fourth edition of this well known text has kept pace with the expanded knowledge in the field of clinical neurology and its basic sciences of neurophysiology and neurochemistry. With the impetus from the lessons learned in the care of brain and spinal injuries in World War II, the ever increasing importance of traffic and highway injuries, and the role of the physician in industry and insurance practice, the scope of Brock's carefully edited text has enlarged. New topics and chapters have been added, and many chapters have been completely rewritten to take advantage of new knowledge, improved diagnostic procedures, and treatment.

Dr. Brock has written the chapter on Traumatic Neuroses (authored in earlier editions by Paul Schilder, who met his death when he was struck down by an automobile) with fine emphasis on the psychodynamic aspects of this important feature of trauma. Psychologic treatment and the use of neuroleptic drugs have been expertly covered. This chapter and the chapter on Simulation (Malingering) should be read by all physicians engaging in medicolegal practice.

An admirable chapter has been written on Concussion and Contusion of the Brain and Their Sequelae. The author does much to clear up confusion existing in the understanding of the nature of concussion and the limits of its definition. A chapter of monographic proportions deals with Herniations and Protrusion of Intervertebral Disc Tissue.

It seems presumptuous, perhaps, to pick out isolated chapters for special mention when each of the 31 contributors is well known for his contributions as investigator, author, teacher, and specialist in the field he has covered.

The importance of this timely text cannot be overemphasized when one reads in the *AMA News* (November 14, 1960) that traffic accidents rank third as cause of death and that in 1959 there were 1,400,000 disabling injuries from highway accidents alone. This text should be in high demand.

M.G.M.

Neurology Simplified

by David Joseph La Fia, M.D., 175 pp., Ill., Charles C Thomas, Springfield, Ill., 1960 $6.75.

It is with the best of intentions that a neurosurgeon has written this supposedly practical and painless exposition of clinical neurology. The book is directed to the general practitioner and the medical student in the hope that it will serve to raise their index of suspicion for the presence of neurologic disease. The dust jacket and the introductory comments also imply that it will enable them not only to achieve a desirable competence in neurologic diagnosis but even to arrive at a correct diagnosis in 75% of cases. It is more than doubtful that such will be the case. The 170 pages of this do-it-yourself, rule-of-thumb approach to neurology encompasses directions for history taking, the

technic of the neurologic examination, the applied neuroanatomy requisite for localization, consideration of all the usual special diagnostic procedures, and a running account of the most common disorders of the nervous system. The inevitable superficiality and oversimplification are self-defeating, for these qualities can be as perplexing and discouraging to the novice in the field as is overelaboration of detail. It is this cursory treatment of the subject, as well as a bias toward disorders of neurosurgical interest, that makes the book unsuitable for use by medical students. Furthermore, it contains a number of inaccurate or misleading statements; "Nystagmus is the opposite of extraocular paralysis" is a fair example.

The reviewer shares the author's impatience with the idea that neurology is too esoteric for the general practitioner. There is no reason why the well-educated physician should not feel familiar with neurologic diseases, but this can never be an easy accomplishment. What is necessary cannot be learned from manuals and schemata. It can come only from proper teaching of medical students and house staff in the hospitals. There are far better books than this one to supplement such instruction.

R.B.R.

Inheritance of Glioma

by H. J. van der Wiel, Consulting Neurologist, Municipal Hospital, Gonda, The Netherlands, 275 pp., Elsevier Publishing Co., Amsterdam, 1960. Distributed in the United States by D. van Nostrand Co., Inc., Princeton, N. J. $12.50.

This monograph is written in the Scandinavian tradition of making a whole volume out of data which can be adequately presented in an article of a dozen or so pages. By the same token, it is written in excellent English and provides pleasant reading throughout.

The author's motive in undertaking a study of the inheritance of glioma was "the wish to attempt to prove and describe a predisposition for gliomas and to look for genetic differences between the various types of gliomas . . ." The book begins with the usual detailed review of the literature of the genetics of carcinoma, glioma, and other neoplasms from which, by the way, some recent and important references are missing (for example, *Breast Cancer* by Anderson, Goodman, and Reed, published in 1958). There is also an extensive discussion of the biology of glioma and the relation of status dysraphicus to hereditary defects of the nervous system and other hereditary disorders.

The study sample consisted of 100 patients from The Netherlands in whom the diagnosis of glioma was verified by surgery or autopsy. Of the 5,262 relatives of these patients, 3,557, or 39.5%, were examined by the author. Among the deceased relatives, there were 14 cases in 12 families in which tumor was the primary cause of death; 8 of these tumors were pathologically verified, and 6 were found to be gliomas, 1 medulloblastoma, and 1 meningioma. No pathologic evidence was available for the other 6.

On the most important matter of controls, the study unfortunately does not appear to follow a well-defined experimental design. The controls are merely described as a list of addresses of 100 individuals randomly selected for absence of cerebral tumor. Since no further details are given, the degree of bias introduced in the selection of controls cannot be evaluated. The author and his associates examined most of the 2,827 relatives of the controls and found no cases of cerebral tumors. Compared with the whole population of The Netherlands, the mortality due to glioma in the tumor group was found to be 4 times higher than expected. On the basis of these findings, the author suggests that a dominant factor with very low penetrance or polygenic inheritance may operate in the causation of glioma.

With respect to status dysraphicus, the author is of the impression that lethal dysraphic features were more frequent among the relatives of the propositi than among the general population. He considers this a strong argument in favor of the hypothesis that status dysraphicus predisposes to glioma, but the discussion on this point is not illuminating and mostly irrelevent. Besides, by the author's own admission, no good history of dysraphic stigmata could be obtained from the relatives. In the tumor group, a positive correlation between status dysraphicus and cafe au lait spots was also noted, while none was found in the control group.

The author reaches the conclusion that

status dysraphicus is caused by specific genes which also have significance in the origin of gliomas.

With the exception of the work of Harvald and Hauge, there exist practically no genetic studies of cerebral tumors. Well-collected data, therefore, are particularly welcome. Unfortunately, the study under review is, at best, a very limited contribution. The data are inadequately controlled and analyzed, and, therefore, the conclusions are unwarranted.

N.C.M.

International Review of Neurobiology
edited by Carl C. Pfeiffer and John R. Smythies, Volume 2, 410 pp., ill., Academic Press, Inc., New York City, 1960. $11.

This volume is the second in a projected series of "annual" reviews on progress in neurobiologic research. It contains 9 contributions on a variety of topics: Regeneration of the Optic Nerve in Amphibia by R. M. Gaze (University of Edinburgh); Experimentally Induced Changes in the Free Selection of Ethanol by J. Mardones (University of Chile); The Mechanism of Action of the Hemicholiniums by F. W. Schueler (Tulane University); The Role of Phosphatidic Acid and Phosphoinositide in Transmembrane Transport Elicited by Acetylcholine and Other Humoral Agents by L. E. and M. R. Hokin (University of Wisconsin); Brain Neurohormones and Cortical Epinephrine Pressor Responses as Affected by Schizophrenic Serum by E. J. Walaszek (University of Kansas); The Role of Serotonin in Neurobiology by E. Costa (Galesburg, Ill. State Research Hospital); Drugs and the Conditioned Avoidance Response by A. Herz (University of Munich); Metabolic and Neurophysiological Roles of γ-Aminobutyric Acid by E. Roberts and E. Eidelberg (City of Hope and UCLA); and Objective Psychological Tests and the Assessment of Drug Effects by H. J. Eysenck (University of London).

The variety and scope of the topics enumerated above make it extremely difficult for a single reviewer to do justice to this book. As a first impression, there is an over-all flavor of neuropharmacology and perhaps also of behavioral aspects, but this is an oversimplification and not fair to other chapters of a more neurochemical or morphologic nature. Certainly each chapter is interesting and informative in its own way. Personal background and preferences of any reviewer would naturally favor certain of these over others. This reviewer found some chapters tended to bog down in a mass of drug data and/or experimental observations not particularly well organized or critically appraised. These points seem valid here because of the broad scope of the book and hence the reading audience to which it is directed, in the sense that one would hope for as clear and helpful presentations as possible for those outside the field being discussed.

Bearing in mind the foregoing, the reviewer personally found the chapters on hemicholiniums (agents which interfere with acetylcholine synthesis), on phosphatidic acid (its possible roles in hormone and enzyme secretion and in sodium transport), and on γ-aminobutyric acid among the most interesting. Each is well written and should be reasonably clear to even the nonchemist. Both chapters concerned directly with the evaluation of drugs on behavioral responses (by Herz and Eysenck, respectively) deserve attention because of their concern with the problems involved. Each is difficult reading for the nonpsychologist but still worth the effort in order to gain some insight into this most important field. Perhaps the most generally fascinating chapter is the one on optic nerve regeneration, which presents a neat set of problems in morphology, physiology, and what might be termed neurobiotaxis in its broadest sense. Here is truly an example of neurobiology at its best. The remaining three chapters impressed this reviewer less favorably, largely for reasons outlined in the preceding paragraph. Perhaps the more controversial nature of the problems—ethanol consumption, cerebral catechol amines and schizophrenia, and the role of serotonin—is also a factor.

The book has much of interest to many in the various fields comprising neurobiology. It is not intended by the editors to be comprehensive but to illustrate specific areas of progress and recent interest. No doubt most workers in the fields concerned will derive much from perusal of the book. Certainly the editors and their associates deserve credit for the conception and execution of this volume.

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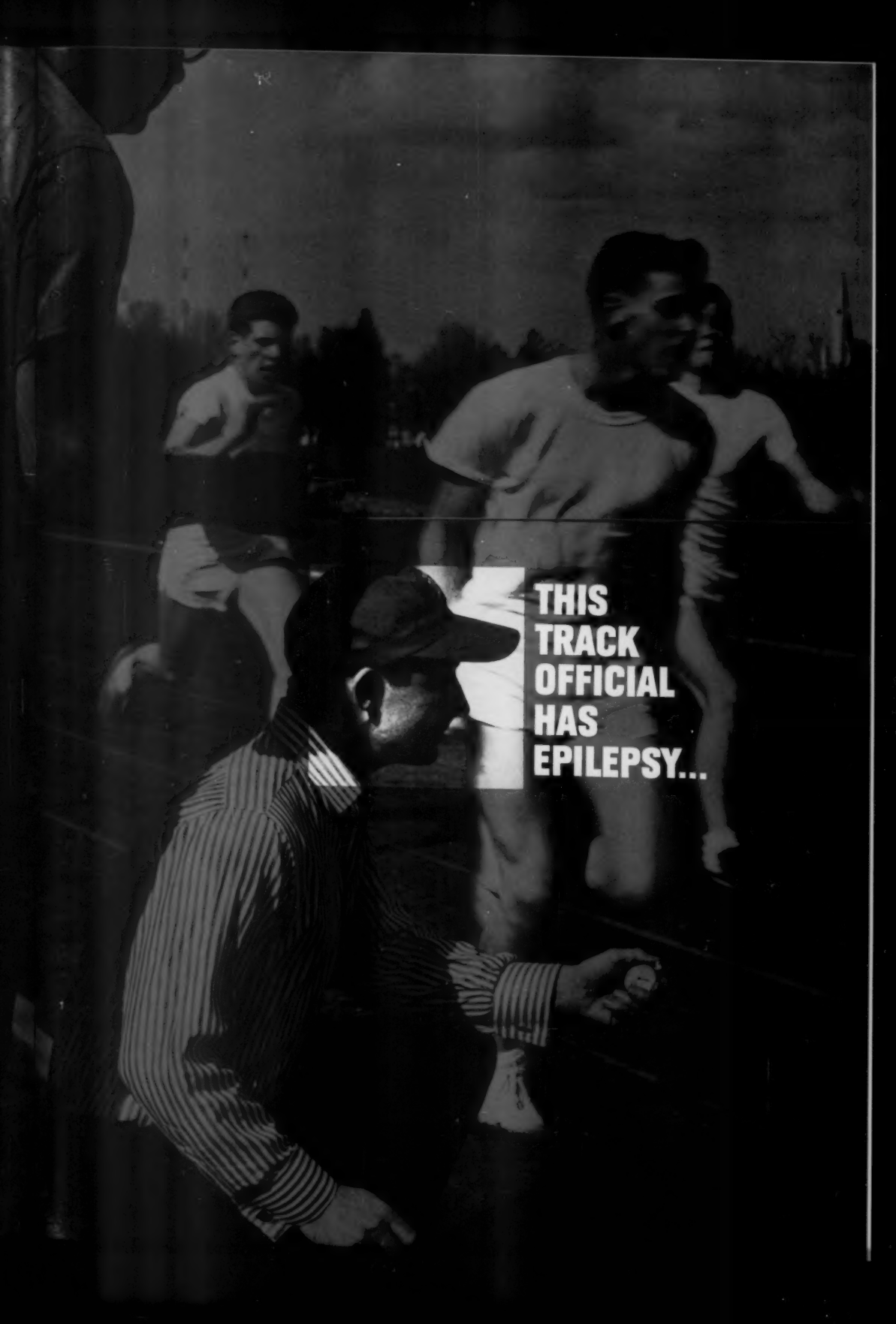
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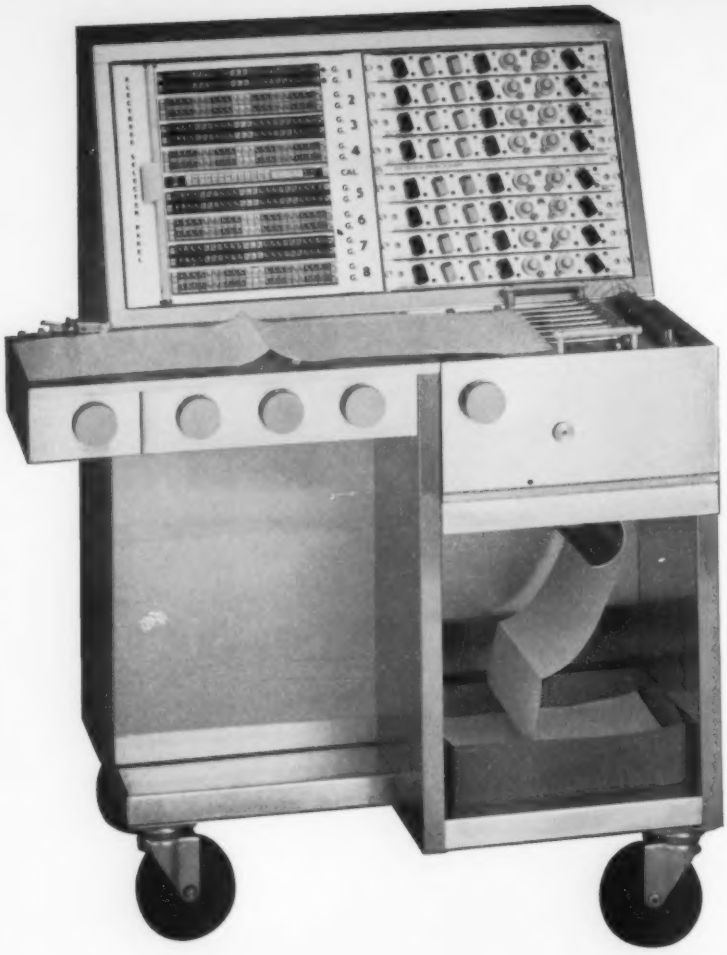

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NEWSLETTER

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JUNE 1961

June 1961

Academy Meets in Detroit

The American Academy of Neurology held its thirteenth annual meeting in Detroit's Sheraton-Cadillac Hotel April 24 through 29, 1961. The activities began with the traditional special courses (April 24 through 26) of A. B. Baker's committee -- an annual event that has gained international renown. The scientific program, opened by the presidential address of Augustus S. Rose, comprised general scientific sessions (April 27 through 29) as well as special programs prepared by the Sections of Neuroanatomical Sciences (Orville T. Bailey, chairman) and of Neurochemistry (Donald B. Tower, chairman). The section sessions were held simultaneously with the general sessions on the afternoons of April 27 and 28. The program of the Section on Anatomical Sciences included a symposium on the hypothalamus, chaired by Ray S. Snider. The general sessions on Friday afternoon, April 28, were held in conjunction with the AAN Child Neurology Section (Charles A. Kennedy, chairman). Among the highlights of the meeting was the presentation of the S. Weir Mitchell Award Essay by Joel Brumlik (Chicago) on Friday afternoon, April 28 -- title of his paper was "On the Nature of Normal Tremor" -- and the delivery of the Robert Wartenberg Memorial Lecture by Macdonald Critchley (London) on "Testamentary Capacity in Aphasia." A total of 42 papers was presented at the general sessions and 20 at the special section meetings; 10 papers were read by title. In addition, there were 16 scientific exhibits; 3 Society exhibits (Muscular Dystrophy Associations of America, United Cerebral Palsy, and the National Foundation); and 14 technical exhibits.... A whirl of social events marked the meeting, beginning with the traditional early-bird party in the Book Casino (Wednesday, April 26) which was sponsored by Parke Davis & Company and terminating in the annual banquet and dance which was held in the grand ballroom on Friday evening, April 28. The AAN Detroit meeting was high caliber and ran smoothly and efficiently due to the careful planning of Joseph M. Foley and his scientific program committee, to Dave B. Ruskin and his convention management and exhibits committee, and especially to Joseph L. Whelan and his committee on local arrangements.... The fourteenth annual meeting of the Academy is scheduled to be held at the Statler-Hilton Hotel in New York City during the last week of April 1962.

Special Courses Reach New High At the thirteenth annual AAN meeting in Detroit, the special courses prepared by A. B. Baker and his committee reached a new high in popularity and registration. There were 761 registrations with 376 physicians and scientists enrolled. The course with the highest registration (114) was Abnormal States in Neurophysiology (J. L. O'Leary); Newer Concepts of Human Cerebral Organization (John S. Meyer, chairman) was second with 91 registrations, which was followed by Advanced Electroencephalography (Frank Morrell, chairman) with 76 registrations, Advanced Child Neurology (Michael E. Blaw, chairman) with 70 registrations, Basic Electroencephalography (Fernando Torres) with 62 registrations, Metabolic Disorders of the Nervous System (Gilbert H. Glaser) with 60 registrations, Neuroradiology (A. L. Sahs) with 53 registrations, Neurochemistry (Maynard M. Cohen and Donald B. Tower) with 52 registrations, The Electron Microscope and the Nervous System (Augustus S. Rose) with 43 registrations, and the Medical Legal Aspects of Neurology (Royal C. Gray) with 36 registrations. In addition, there were 63 registrants in the course for general practitioners (Benjamin Boshes).... For the 1962 meeting in New York City, it is planned to give again 12 courses, about 4 of them repeats and the remainder new courses.

Sahs Becomes AAN President Adolph L. Sahs, Professor of Neurology of the State University of Iowa, became the (1962-64) Academy President in the final phase of the thirteenth annual AAN meeting in Detroit. Dr. Sahs, an AAN member since its inception in 1948, will administer the Academy affairs in Iowa City in conjunction with the AAN Executive Office in Minneapolis. As president, he succeeds Augustus S. Rose of U.C.L.A..... Other officers elected were Joseph M. Foley (Cleveland), President-Elect; Russell N. DeJong (Ann Arbor), First Vice-President; Benjamin Boshes (Chicago), Second Vice-President; and Charles A. Kane (Boston), Secretary-Treasurer. Elected as councilors for two years are Benedict Nagler, Sidney Carter, and Dave B. Ruskin; elected for four years: Fred Plum (Seattle), Richard P. Schmidt (Gainesville, Fla.), and Gilbert Glaser (New Haven). The officers and councilors compose the AAN Executive Board.... Thomas D. Swedien is the AAN Executive Secretary with offices at 4307 East 50th Street, Minneapolis 17, Minn. Mrs. J. C. McKinley, formerly Executive Secretary, is now special administrative advisor to the executive office.

Eleven Neurologists Certified by American Board As a result of the examinations held in March 1961 in New Orleans, 11 candidates were certified in neurology by the American Board of Psychiatry and Neurology. The successful candidates were Angel, R. W., Hines, Ill.; Dyken, M. L., New Castle, Ind.; Flora, G. C., Minneapolis; Goldberg, H. H., New York City; Green, J. B., Media, Pa.; Layton, D. D., Chicago;

Mayer, R. F., Boston; Nelson, J. W., Memphis; Thomas, J. E., Rochester, Minn.; Toole, J. F., Philadelphia; and White, J. C., Jr., Philadelphia.... All inquiries and correspondence related to the American Board of Psychiatry and Neurology should be sent to Dr. David A. Boyd, Executive Secretary-Treasurer, 102-110 Second Avenue S.W., Rochester, Minn.

Haymaker Becomes Director of Life Sciences Near the end of April, Webb Haymaker, at a special ceremony, took the oath of office as the Director of Life Research Facilities and Assistant Director of Life Sciences Research, a position under the Director of the Life Sciences Program, National Aeronautics and Space Administration (NASA), Washington, D. C. According to Haymaker, his position "means responsibility for the life-sciences part of the USA effort in the space field. It includes the 'Man-in-Space' program, radiation hazards in space, the weightlessness problem, life-sciences requirements in landing on celestial bodies, etc., etc." In his new position Dr. Haymaker will be located at the Ames Research Laboratory, Moffett Field, Calif., which is near Palo Alto. He will command a staff of some 200 (60 scientists and 140 supporting personnel), to be built up in the next three years to maximum strength. In going to his new post, Dr. Haymaker feels that he is "not leaving neuropathology, but being given an incomparable opportunity of developing basic research on the nervous system, using numerous modern techniques." Dr. Haymaker will remain at the Armed Forces Institute of Pathology in an unoffical capacity until next October in order to complete his many editorial and other commitments.

Foley Takes New Post in July Western Reserve University President John S. Millis and Dr. Douglas D. Bond, Dean of the Medical School, announce the appointment of Joseph M. Foley as Professor and Director of the Division of Neurology at the School of Medicine, Western Reserve University in Cleveland. Dr. Foley, now President-Elect of the American Academy of Neurology, Professor of Neurology at Seton Hall University College of Medicine and Dentistry since 1959, will assume his new post on July 1. Prior to his appointment at Seton Hall, Dr. Foley, a native of Dorchester, Mass., was Assistant Professor of Neurology at the Harvard Medical School and also Assistant Professor of Neurology at Boston University School of Medicine.... At Western Reserve, Dr. Foley succeeds Clark T. Randt, who resigned last July to join the National Aeronautics and Space Administration in Washington.

McLean Hospital Celebrates Sesquicentennial Anniversary On May 15 and 16, 1961, the McLean Hospital in Belmont, Mass., under the sponsorship of the trustees of the Massachusetts General Hospital, conducted a symposium to honor its sesquicentennial anniversary. Title of the symposium was "A

Multidisciplinary Research Program in a Mental Hospital." The symposium was divided into 2 major parts: A Neurobiological Program (Monday, May 15) and a Behavioral and Clinical Program (Tuesday, May 16). The Monday (May 15) morning sessions, chaired by Raymond D. Adams, comprised presentations on "An Evolving Study of the Chemistry of the Structural Components of the Nervous System" (Jordi Folch-Pi); "Research Program in Microchemical Neuropathology" (Alfred Pope); and "Dynamic Chemoarchitectonics" (Heinrich Waelsch). The Monday afternoon sessions, chaired by Francis O. Schmitt, were devoted to "Implications of Biochemistry to Psychiatry" (Seymour S. Kety); "Biosynthesis of Nucleic Acids" (Severo Ochoa); and "Relevance of Kinds of Scientific Observations to Levels of Understanding" (Rene J. Dubos).... The Tuesday morning program (May 16) was devoted to Behavioral and Clinical Presentations which were chaired by Talcott Parsons and Eric Lindemann. Among the participants were Alfred H. Stanton, Charles Fisher, J. D. Benjamin, Mark D. Altschule, Neal E. Miller, and Robert F. Bales.... A sesquicentennial dinner and reception (by invitation) was held at the Harvard Club on Monday, May 15.

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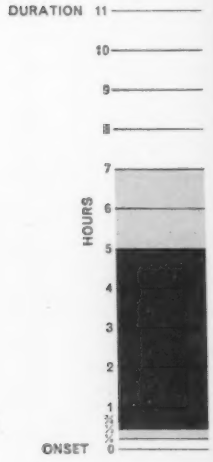

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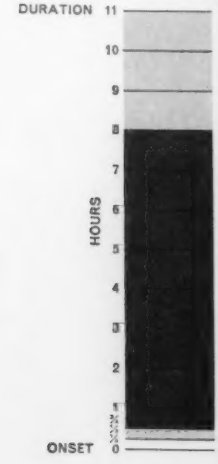

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References: 1. J. D. Young, Jr., W. S. Kiser and O. C. Beyer, **Antibiotic Med. & Clin. Therapy**, 6 (Suppl. 1), 53, 1959. 2. W. A. Leff, **ibid.**, p. 44. 3. R. E. Bagdon, L. O. Randall and W. A. Leff, **Ann. New York Acad. Sc.**, 82 (Art. 1), 3, 1959. 4. J. C. Elia, **ibid.**, p. 52.

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References: 1. Kruse, W.: Dis. Nerv. System 21:79, 1960. 2. Ayd, F. J., Jr.: Clin. Med. 6:387, 1959. 3. Brock, S. (Moderator): Bull. New York Acad. Med. 32:202, 1956. 4. Boshay, L. J., and Boshes, L.: Postgrad. Med. 27:602, 1960.

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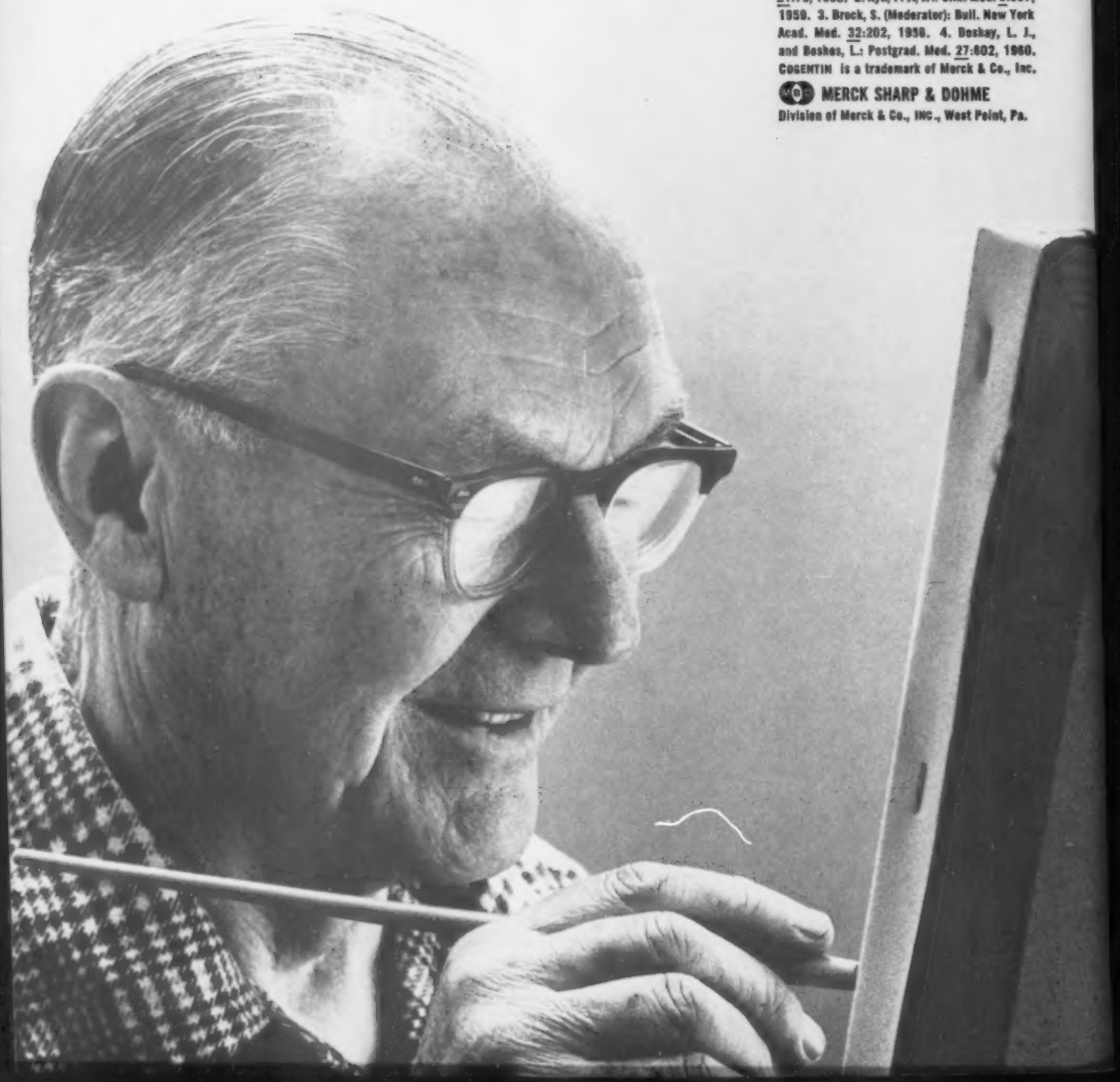
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